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MODERN MEDICINE

ITS THEORY AND PRACTICE

IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS

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VOLUME I

BACTERIAL DISEASES—DISEASES OF DOUBTFUL OR UNKNOWN ETIOLOGY—NON-BACTERIAL FUNGUS INFECTIONS—THE MYCOSES

SECOND EDITION, THOROUGHLY REVISED

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PREFACE

THE wide appreciation of *Modern Medicine* by the profession, as shown by the rapid exhaustion of the first edition and a demand for a revision within the short period of six years, is a source of sincere gratification to the editors and to the publishers.

The revision has been thorough, and certain important changes have been made.

The introductory chapter, the historical sections, the article on the biology of the mosquito, Professor Adami's contribution on "Inheritance and Disease," the introductory section on protozoa, and the article on life insurance have been omitted. Though important, these subjects have not undergone very radical changes, and can be referred to in the first edition.

On the other hand new, or practically new, sections will be found on Pellagra, Beriberi, Trypanosomiasis, Malta Fever, and Dr. Thomas Lewis has contributed a special section on electrical diagnosis in cardiac diseases. As a rule, the condensation has been especially in the etiological and pathological portions, and increased stress has been laid on diagnosis and treatment. Throughout, every article has received from the authors careful and complete revision.

By a general condensation, an increase in the size of the page, and by augmenting the number of pages in each volume, it has proved feasible to reduce the number of volumes from seven to five without impairing the practical character of the work.

The editors promise as little delay as possible in the issuing of the volumes.

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INFECTIOUS DISEASES

CHAPTER I

INTRODUCTION TO THE STUDY OF INFECTIOUS DISEASES

By LUDVIG HEKTOEN, M.D.

Certain minute organisms develop, which the eyes cannot see, and which (being disseminated) in the air enter into the body by way of the mouth and nostrils, and give rise to serious ailments.—VARRO, 116 to 27 B.C.

THE GENERAL NATURE AND SPECIFICNESS OF INFECTIOUS DISEASES

By infection we understand the entrance into the body of living agents, capable of multiplication, which then cause disease.[1] It is true that chemical substances of bacterial origin may produce the symptoms of certain infectious diseases, without infection being present in the usual sense. Experimentally the symptoms of diphtheria and tetanus are produced readily in susceptible animals by the injection of sterile toxins of the corresponding bacteria. Disease so produced is, however, not communicable in the sense that infectious diseases are, because the toxin is incapable of multiplication.

The conception of the specificness of the causes of infectious diseases arose early in the history of medicine. Leprosy, scabies, and hydrophobia were held to be transmissible diseases in early times. Later the observations on immunity and immunization helped to establish the individuality of smallpox, measles, and scarlet fever. The fact that survival of an attack of one disease protected against further attacks of that disease only, and against no other, as well as the results of inoculation in smallpox, pointed most clearly to the existence of specific causes. But only in modern times has the existence of a specific agent been postulated for each infectious disease.

The earlier efforts to demonstrate the microbic causes of infectious diseases—1830 to 1870 about—met with great obstacles both from imperfect technical methods and the erroneous doctrine of spontaneous

[1] In this article the strictly microparasitic infections alone are considered.

generation and the deductions based thereon; namely, that microbes present in the lesions of infectious processes were the products and not the cause of the diseases. When the doctrine of spontaneous generation was overthrown by Pasteur and others, there followed a period during which it was taught by some that the same germ was capable of existing in numerous forms endowed with different functional powers. But the efforts to demonstrate the truth of this statement by experimental transformation of the harmless hay bacillus into the anthrax bacillus failed, and such views soon lost support.

In the meantime Pasteur demonstrated that certain forms of fermentation and decomposition are associated with definite organisms; and the introduction by Koch of solid media for the pure culture of bacteria was another long step forward in the establishment of the specificness of infectious agents. A means was now given for the careful study of the properties of bacteria, and the specific cause of many infectious diseases was studied, and in several instances the etiological role established completely in accord with Koch's well-known laws. Very soon further evidence of the specificity of infectious microbes was secured, as the mechanisms of their action, and the specific nature of the reactive products—antisubstances—in the infected organism were subjected to careful study.

Modern studies of immunity have established the distinct and permanent individuality of infectious microbes, even in the case of those that cause inflammations now in one organ, now in another; and we have every reason to believe that an infectious disease that differs from other infectious diseases has its own peculiar specific cause.

INFECTIOUS AGENTS

By pathogenic microörganisms we understand low forms of life that possess the power of causing infections. The pathogenic microörganisms belong to various classes: Some, like fungi, are low forms of vegetable life; the protozoa are unicellular forms of animal life; while the bacteria occupy a position midway between these two groups, resembling the fungi in their mode of nutrition, and flagellate protozoa in that some possess a locomotive apparatus consisting of flagella. In addition it has been shown that certain infectious diseases are caused by agents that, whatever their nature, pass through filters that hold back bacteria (filterable or ultramicroscopic virus).

Pathogenic Bacteria.—In comparison with the endless number of saprophytic varieties, the number of pathogenic bacteria is very small. Of the numerous vibrios, for instance, practically only one, namely, the cholera vibrio, is pathogenic for man.

From their parasitic relations, pathogenic organisms fall into three groups, namely: (1) Obligate parasites, which develop only within a living host (like the bacillus of leprosy). (2) Facultative saprophytes—microbes that are ordinarily parasitic but able to grow outside the body under special conditions. The majority belong to this group, but there

is no sharp distinction between obligate parasites and facultative saprophytes. The tubercle bacillus, for instance, may be cultivated artificially; but it is doubtful if it grows outside the body under natural conditions. We are constantly learning that microörganisms heretofore regarded as obligate parasites may be grown successfully through many generations on artificial media, *e. g.*, the spirillum of relapsing fever, the *Treponema pallidum*. In these two groups the adaptations to parasitic life are highly perfected, and in some, perpetuation is dependent upon continuous transmission from host to host. (3) Facultative parasites—saprophytic organisms capable of some degree of parasitic existence, but so far as perpetuation of the species is concerned it appears to be a matter of little importance whether they invade the living body or not (*B. tetani*, *B. aërogenes capsulatus*). These forms are regarded as the result of a phylogenetic parasitic adaptation. Whether all bacteria capable of so adapting themselves have done so already, so that no new disease will arise from new adaptations, is an interesting subject for speculation.

Pathogenic Protozoa.—Important infectious diseases in man and animals are caused by protozoa, *e. g.*, malaria, amœbic dysentery, trypanosomiasis, piroplasmosis. The study of pathogenic protozoa and their products has been confined so far within somewhat narrow limits because of our inability to grow these microörganisms in pure cultures on artificial media. However, decided progress is being made in overcoming this obstacle. In 1901, Lignieres observed that proliferation of *Piroplasma bigeminum* may be obtained in defibrinated blood. He succeeded in obtaining subcultures to the fifth generation by inoculating "hemoglobinemic serum." In 1903 Novy and McNeal demonstrated that rat trypanosomes can be grown artificially on agar mixed with defibrinated rabbits' blood, and soon after that many other trypanosomes can be cultivated *in vitro* in the same way.

Ultramicroscopic or Filterable Virus.—The chief reason for the invisibility of the agents concerned in many diseases of unknown etiology is their ultramicroscopic size. If the influenza bacillus were four to five times smaller it could not be seen with the ordinary microscope, which does not reveal bodies smaller than 0.2 μ. The organism of peripneumonia is so minute that it is barely visible; it occupies the borderline between the visible and the invisible.

It has been shown that, at least at some stage of their development, the viruses of foot-and-mouth disease, peripneumonia, rinderpest, sheeppox, chicken-typhus, horse-sickness, epithelioma contagiosum in fowls, yellow fever, hydrophobia, hog cholera, dengue fever, and poliomyelitis, as well as a number of other diseases in animals, pass through various filters ordinarily regarded as impermeable to the smallest known bacteria. Some of these diseases are transmitted by living insects. The filtrates give no morphological sign of containing visible corpuscular elements (except in peripneumonic virus), are virulent, and the diseases so caused are transmissible, and hence truly infectious. The virus of pleuropneumonia and of certain other animal diseases of this group have been cultivated artificially. The list of diseases caused by filterable

viruses has been growing steadily since 1898, when Loeffler and Frosch published their pioneer work on foot-and-mouth disease, and no doubt further discoveries of great interest will be made in this field.[1]

THE SOURCE OF INFECTIOUS AGENTS, AND THE WAYS AND MEANS OF INFECTION

It has been pointed out that only few pathogenic germs lead a saprophytic existence regularly, and at present the most important source by far of the microbes that cause infection is the sick man or animal from which the microbe may pass to other individuals and start new infections either by direct or indirect transfer.

Occurrence of Pathogenic Bacteria on Healthy Human Beings.—So long as microbes remain wholly on the surface of the body, either externally or internally, they are not able to produce disease. The skin and the mucous membranes which communicate with the external air constantly harbor bacteria capable of causing disease under suitable conditions. The principal pathogenic bacteria on the skin and mucous membranes of man are streptococci, staphylococci, pneumococci, colon and influenza bacilli, and certain pathogenic anaërobes. Streptococci and pneumococci of undoubted pathogenic possibilities are present on the tonsils. Certain staphylococci always occur on the skin.

Diphtheria bacilli may be found in the throats of normal persons, especially in connection with outbreaks of the disease. Meningococci occur in the nose and throat in a considerable percentage of persons in close contact with patients suffering from epidemic cerebrospinal meningitis. In outbreaks of typhoid fever, Asiatic cholera, and dysentery, when the bacilli of these diseases are disseminated freely, it is not unusual to find them in the intestinal contents of individuals who do not suffer from infection. Persons who have recovered from typhoid fever may harbor typhoid bacilli in the urine, bile, and feces for months and even years. Even persons who so far as known have not had typhoid fever may be chronic carriers of the bacilli. There is evidence that epidemic poliomyelitis also may be spread by means of healthy carriers. These facts illustrate the manner in which healthy persons may convey specific infectious germs to those that are susceptible, and the importance of such "infection carriers" in spreading infectious diseases is now fully understood. Their recognition and control constitute a serious problem in preventive medicine.

Transmission of Infection by Animals.—Animals may cause human diseases in three different ways. In the first place, they may suffer from diseases directly or indirectly transferable to man, *e. g.*, anthrax, tuberculosis, glanders, pest, paratyphoid infection, etc. In the second place,

[1] For a succinct review of the filterable viruses see Wolbach, *Boston Med. and Surg. Jour.*, 1912, clxvii, 419. Concerning cultivation of virus of chicken-typhus see Landsteiner and Berliner, *Centralbl. f. Bak.*, 1912, i, Orig., lxvii, 165. Concerning cultivation of the virus of epidemic poliomyelitis see Flexner and Noguchi, *Jour. Amer. Med. Assoc.*, 1913, lx, 362.

animals, especially flies, may act as mechanical carriers of germs in such a way that contact or food infection of human beings occur. Suctorial insects may transfer infective material from the sick to the well. This is illustrated by trypanosomiasis, which is transferred by certain flies; by dengue, which is communicated by a mosquito; by Rocky Mountain spotted fever, which is transferred by a tick; by typhus fever, which is spread by lice; and by bubonic pest, in the transmission of which from rats and probably also other rodents fleas play an important part. In the third place, certain animals, especially mosquitoes, act as intermediary hosts for pathogenic protozoa and organisms of as yet unknown nature, which here pass through developmental cycles and acquire infectious powers so that they cause disease when deposited again in the tissues of susceptible persons, as in malaria and yellow fever. The first demonstration of an intermediate host of this kind was made by Theobald Smith and Kilbourne, who showed that the parasite of Texas fever in cattle is transmitted by a tick. Their work paved the way for the demonstration of the role that the mosquito for some time had been suspected of playing in malaria and also in yellow fever.

Aërial Infection.—Infectious microörganisms may be deposited on the ground or floor, on clothing, and other articles. There is evidence that the acute exanthematous diseases, wound infections, pest, diphtheria, typhoid fever, and other diseases, may be carried by infected clothing and other articles. In most of these cases it concerns the conservation of microbes in virulent form rather than actual multiplication; cholera and typhoid bacilli may multiply perhaps in fecal masses deposited on clothing. Bacteria may be carried in the air also. Cornet called our notice to the dangers of dried tuberculous sputum. In 1897 Flügge established that air may convey bacteria not only when dry, as dust, but also in fine droplets of sputum or moisture.

True *dust infection* requires that the organism withstand drying in the air to the extent that it can be whirled about and carried for some distance. Of course, strong currents, mechanical disturbances of accumulated matter, "dry dusting," violent shaking and rubbing of handkerchiefs and other contaminated articles, may set in motion larger particles containing infectious materials, but these would rapidly settle down, when it is true, they might cause infection from direct contact; smaller particles of completely dried material may remain suspended for three or four hours, however, and herein lies the chief danger of this mode of infection.

Largely upon the basis of results obtained by Neisser, Gotschlich divides bacteria with reference to their power to communicate disease when dry as follows:

1. Bacteria that are not viable in air-dried dust and which consequently cannot disseminate disease in dust: cholera vibrio, gonococcus, pest, and influenza bacilli.

2. Bacteria that withstand drying and may convey disease when carried by such air currents as occur in ordinary houses (1 to 4 mm. per second): meningococcus, pyogenic cocci, *Bacillus pyocyaneus*, tubercle bacillus, tetanus bacillus, and anthrax spores.

TABULAR SUMMARY OF THE WAYS AND MEANS OF INFECTION IN THE MOST IMPORTANT HUMAN INFECTIOUS DISEASES (MODIFIED AFTER GOTSCHLICH).

Disease.	Direct contact with sick.	Carriers.	Indirect contact.	Drinking water.	Food.	Air infection.		Soil.	Animals.		
						Dust.	Droplet.		Intermediate hosts.	Infected animals.	As carriers.
Angina	Common mode	Yes	Yes	....	Yes	Yes	Common mode	....	....	Cows (?)	
Anthrax	Yes	.....	Yes	....	Yes	Yes	Yes	Yes	....	Cattle, sheep	Flies
Cholera	Yes	Yes	Yes: wash-linen, bedding, utensils, etc.	Common mode	Yes	....	....	....	....	....	Flies
Diphtheria	Common mode	Yes	Yes: bedding, wash, playthings	....	Yes, milk	Yes	Yes	....	....	....	Flies
Dysentery (bacillary and amœbic)	Yes	Yes	Yes: especially bacillary — wash-linen, utensils, etc.	Yes: especially amœbic	Yes	....	....	....	....	....	Flies
Erysipelas	Yes	Yes	Yes	....	Yes	....	Yes	....	....	Cows (?)	
Glanders	Yes	.....	Yes	....	....	....	Yes	....	....	Horses	
Gonorrhœa	Essential mode	Yes	Yes, possible								
Influenza	Essential mode	Yes	Yes	....	....	?	Yes				
Leprosy	Common mode	.....	Yes (?)	....	....	?	Yes (?)	....	....	....	Flies
Malaria	.....	Latent cases source for dissemination by mosquitoes	.....	....	....	....	....	....	Mosquitoes.		
Malta fever	.....	.....	.....	....	Goats' milk	....	....	....	....	Goats	
Measles	Common mode	Yes (?)	Yes	....	....						
Meningitis (epidemic)	Common mode	Yes	Yes	....	....	Yes ?	Yes Yes	....	....	....	Flies possibly
Mumps	Yes	Yes	Yes	....	....	....	Yes				
Paratyphoid	Yes	Yes	Yes	Yes	Yes. meat, milk	....	....	....	....	Cattle	

Pest	Yes (pest pneumonic)	Yes	Yes: infected clothing, rags, washlinen, rooms	....	....	....	In pest pneumonia	....	....	Rats, mice, other rodents	Fleas
Pneumonia	Common mode	Yes	Yes	....	....	Yes	Yes				
Poliomyelitis	Yes	Yes	?	....	....	?	Yes	....	....	....	Stable fly
Rabies	Sick animals	.....	.....	....	....	....	....	....	....	Dogs, etc.	
Relapsing fever	Yes (?)	.....	Yes	....	....	....	....	....	....	....	Bedbugs, fleas
Rocky Mountain fever ("spotted fever")	.....	.....	.....	....	....	....	....	....	Ticks	....	Ticks
Scarlet fever	Common mode	Yes	Yes	....	Yes: milk	Yes: scales	Yes				
Syphilis	Only mode	Yes	Yes, possible								
Tetanus	.....	.....	.....	....	....	....	....	Yes			
Trachoma	Common mode	Yes	Yes: handkerchiefs, towels, etc.	....	....	Yes	....	....	....	....	Flies
Trypanosomiasis	.....	.....	.....	....	....	....	....	....	....	....	Tsetse-fly
Tuberculosis	Common mode	Yes	Yes: carpets, handkerchiefs, etc.	....	Yes: milk	Yes	Common mode	....	....	Cattle	Flies
Typhoid fever	Yes	Important	Important	Common mode	Yes	Possible	Possible: typhoidal pneumonia	Yes	....	....	Flies
Typhus fever	.....	.....	.....	....	....	....	....	....	....	....	Lice
Variola	Common mode	Yes	Yes	....	....	Yes	Yes				
Whooping cough	Essential mode	Convalescents dangerous for long time	Yes	....	....	?	Typical mode				
Wound infection	Yes	Yes	Yes	....	Yes	Yes	Important	Yes			
Yellow fever	.....	Latent cases source for dissemination by mosquitoes	.....	....	....	....	....	....	Mosquitoes		

3. Bacteria that withstand drying but are disseminated only by so strong currents as rarely occur in houses: diphtheria bacillus, typhoid bacillus.

Cutaneous debris and other material, conveying measles, smallpox, and possibly scarlet fever, are disseminated in dust. English observers lay great stress on the "aërial convection" of smallpox. In measles and scarlet fever the danger of aërial infection is confined to within a few feet from the patient.

Droplet Infection.—Flügge has demonstrated that in talking, coughing, and sneezing, germ-laden bubbles of mucus and saliva pass out into the air, where they may float about for a time. The distance to which these may pass depends on the force with which they are expelled, the nature of the air currents, and the size and weight of the droplets. Tuberculous patients rarely throw out droplets farther than 1.5 meter, the limit within which association with coughing consumptives is postively dangerous. On account of the viscid character of tuberculous sputum the droplets on drying adhere, and mechanical influences are necessary in order to loosen particles from dry drops. Tubercle bacilli may remain alive for eighteen days in drops that dry in the dark, and for three days in the light.

It is likely that influenza, pneumonia, diphtheria, whooping cough, measles, scarlet fever, and smallpox may be communicated by droplets, and probably also epidemic meningitis and poliomyelitis. Plague pneumonia appears to be spread in this way especially.[1] Streptococci may be expelled to various distances in talking, coughing, and even in rapid breathing, and undoubtedly operative infections may be caused in this way. It is also probable that in hospital wards especially, virulent streptococci and pneumococci may be communicated through droplet infection. Patients with leprous lesions in the nose and mouth may expel large numbers of lepra bacilli in droplets of mucus. Dust and droplet infection is most dangerous by far in closed rooms, railway cars, and shops. In the open it is less likely to occur because of the space, the strong currents of air, and the action of sunshine.

Water-borne Infection.—Water plays an essential role in the dissemination of typhoid fever, cholera, bacillary and amœbic dysentery. It is only exceptionally that actual bacterial multiplication takes place. In India the temperature and amount of vegetable and other material in the waters of the Ganges enable the cholera spirilla to multiply. In most waters in temperate climates the bacteria are able to maintain life for a comparatively short time only. It is said, largely as the result of laboratory experiments, that cholera germs will remain alive in water under "natural conditions" for three months, and typhoid bacilli for four weeks. In the experiments of Jordan, Russell, and Zeit, in which typhoid bacilli were exposed to canal and river waters in sacs permeable to dissolved substances, the bacilli perished, as a rule, within three or four days. It may be that resistant bacteria withstand for a longer period the hostile influences in water.

[1] Strong and Teague: *Phil. Jour. Trop. Med.*, 1912, vii.

Vegetable Matter and Infection.—Undoubtedly the organisms causing actinomycosis, blastomycosis, sporotrichosis, and aspergillosis may occur on vegetable matter. In actinomycosis awns and bits of straw and grass have been found in the lesions, clustered about with ray fungi.

The Soil and Infection.—According to Pettenkoffer, the subsoil played an essential part in the dissemination of infectious diseases; but this view has been abandoned because pathogenic germs do not reach deep down. Experimentally it has been found that typhoid and cholera bacteria may retain their viability for some time when deposited in the superficial layers of the soil. Anthrax bacilli may live for a long time in the ground, where they pass into spore forms which may infect susceptible animals. The upper layers of manured soil also harbor pathogenic anaërobic organisms, of which the most important are the tetanus and the gas bacilli.

Food and Infection.—Various pathogenic bacteria may occur in food. These may be derived from animals, as tubercle, anthrax, glanders, and paratyphoid bacilli, and streptococci. Food, especially milk, originally quite pure, is frequently contaminated on its way to the consumer. Milk is a peculiarly dangerous medium because it furnishes conditions favorable for microbic multiplication. Typhoid fever, scarlet fever, diphtheria, tuberculosis, foot-and-mouth disease, and streptococcus infections may be spread by milk. The germs may reach the milk either from the cow, as in the case of tubercle bacilli, or as the result of contamination from human sources. Extensive epidemics of streptococcus infection ("epidemic sore throat") have been traced to the milk supply.[1] Oysters and other shellfish may convey typhoid bacilli from polluted waters. In cholera epidemics, especially in the Philippine Islands, the disease was spread through food to a larger extent than by contaminated water. Non-infective but toxicogenic saprophytes may multiply in milk, dairy products, meat, and fish, which, when consumed, thus may cause severe—often fatal—forms of acute intoxication. Paratyphoid bacilli play an important role in meat poisoning, and in some of these cases the symptoms are typhoid-like; other cases are more acute, and here it appears to concern the meat of cattle infected during life. Malta fever is communicated by the milk of infected goats.

ROUTES OF INFECTION

Pathogenic microörganisms may enter the body by its external and internal surfaces. Bacteria may find conditions favorable for lodgement in the gland ducts and hair follicles of the skin. It has been shown that when *Staphylococcus aureus* and other bacteria are rubbed into the skin, they may enter gland ducts and cause furuncles. In nursing women staphylococci enter the milk ducts. Pest bacilli cause infection when applied to the shaven skin of guinea-pigs, but the possibility of minute wounds cannot be excluded. Minute wounds no doubt often

[1] See Miller and Capps: *Jour. Amer. Med. Assoc.*, 1912, lviii, 1848.

form points of entrance for infection; this is thought to be the rule in bubonic pest; but the actual wounds are rarely demonstrable, the bubo being the primary localization. The pulling out of hair on the upper lip is sometimes followed by exceedingly virulent forms of staphylococcus infections (carbuncle of the lip). It has been demonstrated that when bacteria (anthrax bacilli) enter the bloodvessels of the skin general dissemination occurs within a few moments. The removal of tension by open treatment and drainage greatly lessens the danger of infection through wounds. Crushing wounds are dangerous, and clotted blood in the depths favors the development of tetanus; contused and crushing wounds in general are favorable to anaërobic infection. Healthy intact granulation tissue offers protection to ordinary infection. In addition to ordinary wound and septic infections, the skin is the place of entrance for the diseases communicated by the bites of insects.

In spite of the protection offered by the tears, the conjunctiva is frequently the seat of local infections with various organisms, *e. g.*, the pyogenic cocci, the gonococcus, etc. The experiments of Römer indicate that general infection probably does not occur from the conjunctiva, but by the nasal mucous membrane, to which the organisms are carried through the tear ducts. Small epithelial lesions caused by dust are favorable to local conjunctival infections, but gonococci infect the intact conjunctiva of newborn children.

The loose structure, the great extent of the numerous recesses and folds, and the lymphatic tissues of the nasopharyngeal mucous membrane, render it an important entrance point for infectious organisms. From the nasal mucosa microörganisms may pass directly into the meninges, and in this way it is thought that epidemic and other forms of meningitis and also poliomyelitis may originate. It also seems possible that organisms may find their way to the cerebrospinal membranes by way of the blood. Infections may extend to the middle ear through the Eustachian tube. The nasal lining may receive infection from the conjunctiva, and the German pest commission found that in rats general infection with pest bacilli occurs with great readiness from the intact conjunctiva and from the nose. Leprosy and glanders commonly develop primarily in the nasal mucosa. The elimination of lepra bacilli in enormous numbers, in nasal mucus, points to this as one source of dissemination of this disease.

The lining of the mouth is quite resistant to infection, which is hindered also by the bactericidal and mechanical action of the saliva and mucus. In the newborn, in whom the epithelium is delicate, a mild form of gonococcal infection of the mouth may occur. When vital resistance is reduced, conditions arise in the mouth and throat that favor the development of ulceromembranous and necrotic (noma) processes in which anaërobic bacteria take part. The oral mucous membrane is the most common seat of primary actinomycosis, which probably develops from the implantation of the organisms with bits of straw in the gums. The tonsils are important points of entrance of many infections, due, at least in part, to their exposed position, their deeply corrugated surfaces, and the imperfect epithelial lining. Strep-

tococci and pneumococci occur upon the surface normally. The tonsils are the usual seat of invasion of scarlet fever and diphtheria, which are associated with a more or less well-marked streptococcal angina. Rheumatic fever, infectious osteomyelitis, and obscure general infections are often traceable to the tonsils because of the initial angina. Undoubtedly the tonsils are the most important source of the terminal streptococcus invasion that occurs commonly, especially in smallpox and scarlet fever. While primary tonsillar tuberculosis appears to be rare, the researches of Harbitz show that the tonsils and other pharyngeal lymph nodes may be points of entrance for tubercle bacilli in early life.

Forced inspiration may suffice to carry pathogenic germs from the mouth into the finer bronchi. Flügge and his co-workers have shown that bacteria—*B. prodigiosus*, tubercle bacilli—when inhaled either in artificial spray or dust, or in minute droplets, may be carried into the bronchi and pulmonary alveoli. Undoubtedly inhalation infection plays an important role in the various pneumonias. In some cases it is difficult to distinguish between pulmonary infections from without and those by way of the blood or lymphatic system. Paralysis of the cilia of the bronchial epithelium from cold and other causes has been suggested as predisposing to bronchopulmonary infection. The inhalation of dust particles aids the development of infection by causing minute injuries to the epithelium.

The gastric mucous membrane is resistant to infection on account of the gastric juice, which, when normal, may destroy bacteria or at least hinder their development in the stomach. Koch and others found that feeding sheep with spore-free anthrax bacilli gave negative results, whereas feeding with spores resulted in anthrax. The cholera vibrio is especially susceptible to the acid gastric juice, the typhoid bacillus less so; but when the stomach is empty, or the seat of digestive disturbances, both these organisms may pass through unharmed. The gastric as well as the pancreatic juices destroy diphtheria and tetanus toxins.

Numerous important infections have their point of entrance in the intestines, *e. g.*, cholera, typhoid, dysentery, and, in animals, anthrax, chicken cholera, and various hemorrhagic septicemias. In cholera and bacillary dysentery the intestinal mucosa is the only point of localization, and it is probable that typhoid bacilli commonly enter the body by way of the lymph nodes in the intestinal mucosa. This selective invasiveness is difficult to explain. While cholera vibrios and dysentery bacilli have special affinity for the intestinal mucosa, the bacilli of tetanus and of emphysematous gangrene, which often occur in the intestines, do not penetrate the normal intestinal epithelium. Under pathological conditions and after death the gas bacillus may pass into the tissues and the blood, and most cases of "foamy organs" are due to agonal or post-mortem invasion. Somewhat similar conditions obtain with reference to the colon bacillus, which, however, probably has a greater invasive power. Tubercle bacilli may be absorbed from the gastro-intestinal tract, and the primary localization may occur in the neighboring or remote lymph nodes and possibly the lungs without necessarily leaving any lesions at the point of entrance. When tubercle bacilli are fed to

animals they pass quickly through the intact mucous membrane into the chyle vessels and thoracic duct (Ravenel).

The genitals are the special seat of gonorrhœal and syphilitic invasion. The gonococcus is able to penetrate into the intact mucous lining of the urethra. The vagina is well protected against infection not only by its squamous epithelium, but also by the strongly bactericidal action of its acid secretion (Döderlein, Krönig, and Menge). After parturition the female genital canal offers favorable chances for infection.

We observe that many organisms cause infection only when introduced in a certain way or localized on particular parts. Almost all pathogenic germs show predilections for particular ports of entry, although many are able to use various channels. The reasons for these interesting adaptations must be sought in the biochemistry of the microörganisms and tissues in question.

It is interesting to note that those parts to which an organism is more or less specifically adapted may contain the same microbe or closely related forms, often but not always, in an attenuated state, and usually harmless to the individual, though often capable of causing infection in others. Examples are the occurrence of diphtheria bacilli and of pseudodiphtheria bacilli in normal throats; of pneumococci and streptococci in the throat; of influenza-like bacilli in the respiratory tract; and of typhoid and paratyphoid bacteria in the intestines.

The bacillus of leprosy has particular affinity for nerves. Tetanus and hydrophobia develop from wound infections, and the symptoms become apparent when the tetanotoxin and the agent of hydrophobia have penetrated into the central nervous system. We know that there is a strong chemical affinity between tetanotoxin and the neurocytes.

By *germinal infection* is meant an infection of the embryo by an agent conveyed by the ovum or the semen. Syphilis is believed to be transmissible to the fetus by the sperm as well as by the ovum, but some claim that the mother is always the source of congenital syphilis. There is no satisfactory evidence that tubercle bacilli may be transmitted by germinal infection. Pathogenic microbes may pass from mother to fetus by way of the placenta. Intra-uterine or placental infection of the fetus has been observed in smallpox, measles, scarlet fever, syphilis, typhoid fever, relapsing fever pneumonia, anthrax, pyogenic infections, dysentery, and tuberculosis. In animals the organisms of chicken-cholera, glanders, symptomatic anthrax, anthrax, tuberculosis, etc., are transmissible by way of the placenta, but on the whole this form of infection is quite exceptional.

The claim by Baumgarten that tuberculosis in the offspring of tuberculous mothers is the result of an intra-uterine invasion, the bacilli remaining latent in the child, has not received general support. The number of authentic cases of congenital tuberculosis is still small, although the list is growing.[1] Harbitz has shown that there may be latent animal-virulent tubercle bacilli in normal human organs, but the determination of the duration of such latency presents great difficulty on account of the ever-present opportunities for postnatal invasion.

[1] See Warthin and Cowie: *Jour. Infect. Dis.*, 1904, i, 140.

THE DISSEMINATION OF PATHOGENIC GERMS IN THE INFECTED BODY

In their distribution in the body the microörganisms differ greatly. The most perfect example of local distribution is furnished by the tetanus bacillus, which, when introduced into the tissues, causes only slight local changes and exhibits practically no invasive powers, the symptoms being due to the absorption of toxin. In many infections caused by tubercle bacilli and by the various pyogenic cocci, the process remains local, due most probably to a low degree of virulence of the infecting organisms as related to the immunity of the infected person. While the bacillus of diphtheria and the cholera vibrio remain in a sense local, entering the circulation only exceptionally, both show marked power to extend along the mucous membranes upon which they customarily cause infection.

Infectious germs may be disseminated in the body by extension, as in the invasion of the whole respiratory tract by the influenza bacillus, in the spread of erysipelas, etc. Microörganisms are disseminated also by metastasis, by which is meant the establishment of more or less far spread secondary foci from a primary focus as the chief centre of distribution. In metastasis by the blood, secondary localizations occur in different organs, as in the abscesses of pyemia. Tuberculosis, leprosy, syphilis, glanders, pest, blastomycosis, pneumococcal and pyogenic processes, furnish good examples of circulatory metastasis. Lymphatic metastasis is of frequent occurrence, the primary lesion being often located in the skin or mucous membranes. Upon mucous membranes mechanical factors may convey infectious material from established lesions to new points, as in aspiration pneumonias.

Many diseases caused by filterable viruses contain the virus in the blood (yellow fever, etc.). Malaria and trypanosomiasis are blood infections; in the latter disease, however, the parasites also occur in the connective tissue of the organs. In typhoid fever and in pneumonia bacteriemia probably is present always in the earlier stages.

The factors that determine the invasion of the blood, especially by the organisms that do so only occasionally (streptococci, gonococci, staphylococci), are not clearly understood, but virulence, *i. e.*, the power to resist and overcome the phagocytic and other anti-infectious powers of the blood—undoubtedly plays a most important role. Both microbic virulence and the resistance of the body are variable conditions made up of complex factors that are difficult or impossible to analyze completely in a given case. As microbes are distributed in the body some show a distinct preference for certain tissues. Thus the lepra bacilli seek out the nerves and nervous tissues; the virus of hydrophobia has a special predilection for the nervous system; the gonococci and streptococci tend to localize especially in the joints; meningococci thrive best in the leptomeninges, etc. This affinity may be surmised to depend on subtle chemical attractions between constituents in the microbes and the cells.

THE ELIMINATION OF INFECTIOUS MICROBES AND MICROBIC LATENCY AFTER INFECTIONS

Accurate knowledge of the ways in which the agents of infectious diseases are discharged from the infected body is of great value in the use of intelligent measures to render persons with communicable diseases or their agents harmless to others. As pointed out by Theobald Smith, passage to new hosts is essential in order to perpetuate parasitic species of microbes. There are two distinctly different methods of elimination: (1) Immediate, from the morbid focus by way of pathological products; and (2) indirect, by means of the circulating blood through normal secretions and excretions; or as in the case of some protozoa with highly specialized avenues of entry and escape, through some insect.

In direct elimination the disease must communicate with the outside of the body. This is the case in surface infection of mucous membranes. Here the places of entry, multiplication, and exit often coincide. Examples are seen in conjunctivitis; infections of the nasal mucous membranes (lepra, diphtheria); of the tonsils and pharynx (diphtheria, scarlet fever); of the laryngeal and bronchial (pulmonary) membranes (tuberculosis, pneumonia, influenza, and whooping cough); of the intestinal tract (tuberculosis, typhoid fever, dysentery, and cholera); of the genito-urinary passages (gonorrhœa and tuberculosis). In this class belong also local and general infections associated with lesions in the skin (tuberculosis, suppurations, blastomycosis, sporotrichosis, syphilis, smallpox, measles, and scarlet fever).

Cleansing of the mucous membranes (especially of the respiratory and oropharyngeal) of the materials which they convey is one of the great problems in the prevention of infectious diseases. Disinfection of the discharges from the urinary and intestinal tracts is a simple matter compared to the disinfection of the sputum, visible and invisible, in all the conditions in which it may contain virulently active infectious agents.

In the process of elimination of pathogenic bacteria, especially from deeply situated localities, there is danger of auto-infection, local as well as general, as illustrated well by tuberculosis.

In the second (indirect) form of microbic elimination two conditions have to be met: The microbes must reach the general circulation, and they must pass the epithelial barriers of glandular organs and mucous membranes. Microbes which enter the blood and survive may be eliminated in the urine and otherwise. It appears that some form of lesion is necessary in the kidney in order that bacteria may pass from the blood to the urine. Bacteria are also eliminated from the circulation by way of the bile, and, experimentally at least, certain bacteria are eliminated by the intestinal mucous membrane. As regards the elimination of bacteria from the blood by the glands of the skin, investigations have given contradictory results. Tubercle bacilli frequently occur in the milk of cows with but limited tuberculous lesions not necessarily located in the udder. The agent of rabies is eliminated freely in the

salivary secretions, which explains the infectiousness of the bites of rabid animals.

Not infrequently it happens some time after an attack of acute infectious diseases, as typhoid fever, localized inflammatory processes develop in which are found the bacteria that caused the original infection. A variable period may intervene between the primary disease and the localized process. This survival of bacteria is difficult to explain, especially as the patients concerned must be regarded, in a measure at least, as immunized. Perhaps recurrent attacks of erysipelas, of rheumatic fever, and of other diseases are caused by the survival in the tissues of the causative agents, awaiting some specially favorable moment, or the entrance of some new factor, to manifest again their original activity. Malaria also furnishes striking examples of latency in the infected host.

An analogous condition obtains in persons who become infection carriers after attacks of diphtheria, typhoid fever, and other diseases. Here the microbes may persist for a long time on mucous surfaces and in reservoirs like the gall-bladder and urinary bladder without necessarily causing any symptoms indicating their presence. The presence of typhoid bacilli in the gall-bladder is, however, sometimes associated with cholelithiasis, and in the urinary bladder with turbid urine.

Mention may be made of the views of Baumgarten and Behring in regard to the role of latent tubercle bacilli which, entering the body early in life, are assumed to remain inactive for years before occasion suitable for pathogenic action arises. According to Baumgarten the original infection may be intra-uterine; according to Behring it is alimentary, from cows' milk, the bacilli entering by the digestive tract. Neither view seems to have a secure basis of observation or experiment; but tuberculosis in man furnishes many examples of latency and persistence of the bacillus, and recent studies of old, apparently healed tuberculous foci have shown many instances of encapsulated bacilli still capable of causing active tuberculosis, at least in animals. Harbitz has demonstrated latent tubercle bacilli, virulent for guinea-pigs, in the lymph nodes of children, the nodes being normal in structure so far as could be determined.

In general, protozoal parasites tend to persist in the blood of the host for a long time, even after immunity is established. It has been suggested that infective microbes may pass into a latent stage in which they are protected against destructive influences at the same time as pathogenic activity is suspended, in order to secure opportunity to pass to new hosts. Prolonged latency is a striking phenomenon of syphilitic infection.

MIXED AND SECONDARY INFECTIONS

In the concrete case it may be difficult to distinguish between mixed and secondary infections; but, speaking strictly, mixed infection should mean the simultaneous entrance into the tissues of the body of two or more virulent organisms of different species. It is most commonly

observed in local infections of tissues that stand in immediate communication with some of the surfaces of the body which always harbor various bacterial species. In pharyngeal diphtheria, for instance, streptococci enter the tissues of the tonsil so constantly and so early that this form of mixed infection is regarded by some as constant. Analogous conditions are presented by scarlet fever. Bronchopneumonia due to respiratory infection is commonly a mixed infection, pneumococci, encapsulated bacilli, influenza-like bacilli, staphylococci, and streptococci being associated in various combinations. Wound infections are also frequently mixed infections; infections with anaërobic organisms like the gas bacillus, the fusiform bacilli, tetanus bacillus, are usually mixed, one or more of the common pyogenic species being present also.

A secondary infection means the occurrence of a second microbic invasion in a body already the seat of an existing infection. In most cases there is evidence that the primary infection prepares the way for the secondary invaders. Thus all infections associated with destructive and ulcerative lesions of skin or mucous membranes, like diphtheria, variola, typhoid fever, tuberculosis, etc., facilitate secondary infection with microbes, the most important of which normally are present on the surfaces of the body (streptococci, pneumococci, staphylococci, etc.). More than this, we have reason to believe that infectious diseases, like those just mentioned, directly or indirectly reduce the normal powers of the body to resist infection. Smallpox, scarlet fever, measles, tuberculosis, diphtheria, are associated so commonly with secondary infections, especially streptococcal, that the conditions seem to be more favorable for streptococcal infections in these diseases than in health.

Various groupings of associated infections are possible on the basis of the distribution and fate in the body of the microbes.

1. The associated microbes may remain localized, *e. g.*, in mixed local infections.

2. Both primary and secondary invaders are disseminated more or less extensively throughout the body, *e. g.*, tubercle bacilli and streptococci.

3. The primary organism remains localized or undergoes involution, whereas the secondary invaders persist and extend. A good illustration is general streptococcemia secondary to diphtheria, scarlet fever, smallpox, measles, tuberculosis, or cholera. Not infrequently this streptococcemia becomes apparent after the subsidence of the main symptoms of the primary disease. In pneumonia, typhoid fever, influenza, and other diseases, secondary lesions, often of a metastatic character and due to mixed and secondary invaders, may develop after the primary infection has died out.

4. The mixed or secondary invaders remain localized, whereas the chief organism is disseminated. This is illustrated by local suppurative infections in almost all infectious diseases by the superficial pyogenic invasion of tuberculous cavities, the deeper extension being purely tuberculous, etc.

Manifestly the forms of microbic association are manifold. A

secondary infection may be multiple or mixed, and examples are not wanting of the occurrence of mixed or secondary bacterial infections in protozoan diseases, and *vice versa.*

Association of microbes in mixed and secondary infections practically always tends to increase the danger to the patient. In human pathology we have no positive knowledge of one infection being antagonistic to any other infection. Judging from experiments it seems more likely that bacterial associations tend to increase the virulence of one or other of the associated bacteria. Roux and Yersin came to the conclusion that the simultaneous infection with diphtheria bacilli and streptococci results in an increased virulence of the diphtheria bacillus; v. Dungern, on the other hand, concluded that the virulence of the streptococcus was heightened. Experimental tuberculosis assumes a more acute form in the presence of pyogenic bacteria which is in harmony with the fact that in human tuberculosis fresh eruptions of tubercles appear to follow secondary infections. The change that occurs in many infectious diseases with the advent of severe secondary streptococcus infections is an ominous one. Here the effects of the secondary infection are often overwhelming. The occurrence of measles in a tuberculous child is followed frequently by exacerbation of the tuberculosis.

TOXINS, ENDOTOXINS, MICROBIC PROTEINS, AND THEIR SPLITTING PRODUCTS

The effects of infectious microbes are regarded as chemical rather than mechanical in nature. In a few diseases in which there is great multiplication of the infectious agents in the blood, mechanical effects may play some role; and in pyemia infectious embolism is of great importance; but only a few of the results of infection can be explained on purely mechanical grounds. Since the discovery by Roux and Yersin of the specific poison of the diphtheria bacillus in 1888, the intoxication by bacterial products has been regarded as the cause of the changes in the infected body. Specific poisons have not been discovered for most of the infectious germs as they grow in artificial media, and this has been explained as due at least in part to the differences in the conditions about the bacteria when growing artificially and in the animal body. As yet we have no simple reagents to show the presence of toxins and other microbic poisons. This is demonstrable by animal experiment only, and it is in the cases of certain toxins with characteristic effects, such as diphtheria toxin and tetanus toxin, that investigation has made most progress.

At first there was considerable confusion as to the significance of the word *toxin,* but gradually it has acquired definite limitations, although it is often used in a loose way. Toxins in the strict sense are soluble products of biologic origin, probably of protein nature, sensitive to various influences, especially heat, of high toxicity, the toxic effects becoming apparent after a period of latency, and in the susceptible animal body they give rise to the formation of specific antitoxins which

neutralize each the corresponding toxin. Toxins present many points of similarity with organic ferments. Both are sensitive, labile substances of unknown nature. The idea that toxins are ferments was strengthened by the demonstration (Morgenroth and others) that certain ferments, when injected into suitable animals, give rise to specific antiferments.

The most important bacteriotoxins so far known are diphtheria and tetanus toxins, which by themselves alone reproduce the clinical picture of the disease caused by the respective mother cells. *B. botulinus*, *B. dysenteriæ*, *B. pyocyaneus*, staphylococcus, streptococcus, and other bacteria also produce toxins of pathogenic importance; but some of these have only a limited range of activity, *e. g.*, the laking of red blood corpuscles (bacterial hemolysins). Some bacteria produce more than one toxin; the tetanus bacillus produces tetanospasmin and tetanolysin; staphylococci produce a hemolytic and a leukocidal toxin, etc.

Ricin, abrin, robin, and krotin are the phytotoxins which in the hands of Ehrlich were the means of experiments that gave us the foundation of our knowledge of the relations of toxins and antitoxins. Powerful toxins occur also in the venoms and secretions of snakes and other poisonous animals. In these cases the true toxin nature of the substances has been established by the production of specific antitoxin.

That bacterial toxins may circulate in the blood has been demonstrated conclusively. Thus, Brieger produced tetanus in animals by means of an extract from the amputated arm of a tetanus patient, and Nissen found that 0.3 cc. of serum from a tetanus patient caused fatal tetanus in mice. Wassermann and others found in the blood and organs of animals and human beings, dead of diphtheria, substances that in guinea-pigs produce the lesions peculiar to diphtheria toxin. In other infectious diseases the effort to demonstrate specific toxins in the blood has not met with much success. It is now accepted that the action of bacterial and other toxins is dependent on union of the toxin with certain cells. In susceptible animals tetanus toxin is quickly removed from the blood by the nervous tissues, which Wassermann and Takaki found take up tetanus toxin with avidity outside of the body as well.

In the case of other infectious microbes definite soluble poisons cannot be obtained, at least not in such quantities, if at all, as to explain the changes that result, and Pfeiffer advanced the hypothesis that in infections with these germs the symptoms are produced by preformed poisons which are set free only as the germs are destroyed by lysis and other means. This is the endotoxin theory. All microbes are assumed to contain poisonous substances, but the infectious microbes being able to grow in the body for a time at least are able to furnish large enough quantities of poison to cause definite symptoms. Vaughan, Friedberger, and others doubt the existence of the so-called endotoxins and ascribe the symptoms in the diseases in question to the action of more or less transitory split products produced as the microbic proteins are broken up (the anaphylatoxic hypothesis). They have shown that the products of the splitting of foreign proteins in general cause fever, changes in the number of leukocytes, and other disturbances that take place in infectious diseases. In either case the substances acting upon the

microbes are the same, namely, substances of amboceptor-complement, that is, proteolytic nature. The endotoxin conception seems to account better for the characteristic peculiarities of the symptoms and lesions of the different diseases, but it is possible that these differences depend on the rate and extent with which poison is set free and on the various localizations of the microbes. That some of the microbic proteins retain their original character is shown by the specificness of the anti-substances produced. Even if the newer conceptions do not replace the endotoxin hypothesis completely, they serve to emphasize the part that the breaking up of foreign proteins takes in causing fever, metabolic disturbances, and other changes.[1]

NATURAL RESISTANCE AND MICROBIC VIRULENCE

That infection may take place, the specific cause must enter the body and there exercise its pathogenic powers. In the case of pathogenic bacteria normally present on the surfaces of the body without doing any harm, we assume that the bacteria are of a relatively low virulence or invasiveness, and remain harmless until influences arise that either heighten the virulence or in some way remove or diminish the obstacles to invasion. Death is followed almost at once by the invasion of putrefactive bacteria that in life are prevented from entering the tissues. The body possesses various defensive mechanisms against pathogenic microbes, and on the condition of these mechanisms depend the varying degrees of individual resistance (or susceptibility) to the infectious diseases that may attack a given species.

Various species show great differences in resistance to infection. Some have apparently absolute natural immunity to certain microbes. Cold-blooded animals in general are immune to bacteria that are infectious for warm-blooded forms. We know of no spontaneous bacterial disease among cold-blooded animals that is transmissible to man.

In certain species bacterial toxins highly toxic for man are without any effect under natural conditions. Tetanospasmin does not produce spasms in amphibians and reptiles, but in certain species this immunity may be removed when the temperature is raised by artificial means. Avian tubercle bacilli are able to thrive at a temperature of 43.5° C., at which mammalian tubercle bacilli die. In many instances species immunity probably indicates that certain microbes, parasitic in some species, are unable to adapt themselves to parasitic life in other species.

Whether there is true natural immunity of some human races to certain infectious diseases seems to be doubtful. The alleged immunity of pure Africans to syphilis, once asserted by Livingstone, appears explainable as due to lack of opportunity of infection. Acquired immunity has been mistaken for natural immunity; Koch showed that the immunity of Ethiopians to malaria is acquired, and the immunity of the natives to yellow fever in districts where the disease is prevalent is

[1] This subject is discussed further on p. 431

probably acquired. In the absence of acquired immunity some infectious diseases may assume unusual virulence; this is illustrated in the course of measles in peoples hitherto free from the disease.

According to von Pirquet, in regions in which measles is prevalent, susceptibility develops in most nurslings during the first year; the newborn are quite insusceptible. If the mother has not had measles, however, the child is susceptible from the moment of birth. Indeed, it may be infected before birth. Consequently, the insusceptibility of measles must be due to an immunity of maternal origin, and in the production of which milk does not play any part.

Variations in individual susceptibility may be due at least in part to variations in local factors, mechanical and chemical, that serve to protect the various surfaces of the body. The skin is protective because of its impenetrability to bacteria when intact; the constant desquamation of its superficial layers carries away bacteria vegetating therein; the acid reaction of the perspiration is not favorable to bacterial growth; and the ease with which hyperemia develops on slight invitation—*e. g.*, scratching—brings to the surface leukocytes and the microbicidal substances in the blood. The peristaltic movements of the stomach and intestines, coughing and sneezing, the flow of urine, epithelial desquamation, and the normal action of ciliated epithelium, are mechanical means of removal of microbes from various mucous surfaces. The toxin-destroying powers of the digestive juices, the bactericidal effects of gastric juice and other glandular secretions, and the antagonistic action on pathogenic forms of the sparophytes vegetating on mucous membranes, are all protective factors.

As microbes reach the tissues they at once run counter to phagocytes and microbicidal substances. Frequently these protective agencies are concentrated about the point of localization of microbes by inflammatory changes, thereby increasing the local resistance, at the same time as a general leukocytosis may develop. In case some microbes escape into the tissues they are likely to be arrested by the regional lymph nodes and there subjected to similar destructive forces. Normal blood contains substances that render certain infectious microbes fit for phagocytosis and others that cause lysis, and on the content of the blood in either or both of these substances, capable of acting on a given germ, and on the number and quality of the leukocytes, may depend the degree of individual resistance to infection by that microbe.

Normal human blood causes lysis of typhoid, anthrax, dysentery, and other germs in the destruction of which phagocytosis also plays a role, being an even more prominent factor in the destruction of other germs, *e. g.*, streptococci, pneumococci, etc. The phagocytes require, however, that the germs first must be acted on by substances in the body fluids—the opsonins of Wright and Douglas—which make them susceptible of phagocytosis. The importance of leukocytosis is shown by the fact that resistance to various infections may be increased in a non-specific manner by the injection of a variety of substances, all of which produce leukocytosis, local and general. Serum, blood, various proteins (animal and vegetable), spermin, nucleinic acid, broth, urine,

yeast, living and dead bacteria, bacterial substances—*e. g.*, tuberculin —all have been found to act in this manner, and undoubtedly this non-specific increase in general resistance has been mistaken often for specific effects, especially after the injections of sera supposed to contain immune antisubstances.

Experimentally, resistance may be diminished by various means. Artificial diabetes renders animals more susceptible to infection; so does diminished alkalinity of the blood; muscular exhaustion reduces the microbicidal substances in the blood. Reduction of the temperature renders animals abnormally susceptible to infection. In some common diseases the predisposing causes are of great importance. Diphtheria and pneumonia, the specific causes of which are so widely distributed, are largely cold-weather diseases, but the manner in which cold reduces resistance has not yet received a satisfactory explanation. Alcoholism, uremia, venom intoxication, anesthesia, exanthematous and other acute and chronic diseases, overcrowding and unhygienic living, all lower the individual resistance to various infections; but it is not probable that the various factors concerned in these conditions all act in the same way; the hemolytic and other amboceptors in venoms have a strong affinity for complement, the withdrawal of which leaves the body open to certain forms of bacterial invasion. Complements are neutralized readily by a variety of ions and other substances, such as lactic acid, nucleinic acid, bacterial disintegration products, proteins, and organ extracts, so that it is not difficult to understand how the defences of the body may be weakened. Various kinds of poisons, also, may interfere with the phagocytic action of the leukocytes.

In infectious diseases complex reciprocal relations are extablished between the infected and the infecting organisms. The factors concerned may vary on the part of both, not only in different species, but also in different individuals of the same species, and from time to time in the same individual. Various gross conditions may influence the course of infection. We know that experimental infection runs the quicker course the greater the number, the more virulent the bacteria introduced, and also, as a rule, the more directly they enter the circulation or the large cavities. In this case the natural resistance is, so to speak, overwhelmed. Hemorrhagic infiltrations, clots, crushed tissue at the point of entrance, favor the development of severe tetanus, pneumococcus, and streptococcus infections, because the germs here have favorable opportunities for growth and increase of virulence. The great influence of the anatomical location of the point of entrance is shown particularly well by streptococcus infections: in the dense and tense connective tissue of the finger it causes a local inflammation; in the subcutaneous tissue, phlegmon; in the lymph vessels of the skin, erysipelas; in the peritoneum, peritonitis—conditions that differ greatly in their course though caused by the same microbe.

In the establishment, progress, and nature of an infectious disease much always depends upon that property of the microbe concerned called virulence. If we understand by virulence the degree of pathogenic power of which a microbe is possessed, analysis reveals that virulence

in this sense depends on various properties. It is not necessarily synonymous with invasiveness, because toxicogenic bacteria in the strict sense (*B. diphtheriæ, B. tetani*) possess great toxic power and relatively slight or no invasiveness. In these bacteria virulence depends more on the power to produce toxins, and the body responds by the formation of antitoxins, whereas the production of antibacterial substances is relatively insignificant.

In microbes in which the disease-producing substances are assumed to be locked up in the cells or split off from the microbic proteins, and set free only as the germs reach the tissues of the body, virulence is necessarily connected with power to multiply and invade. Virulence may be reduced by different methods, *e. g.*, exposure to sunlight or the addition of chemicals. The virulence of some bacteria may be reduced for one species by repeated passage through members of some other species. The most striking example of loss or modification of virulence is furnished by the virus of smallpox which is reduced to vaccine virus on passage through calves.

As yet we possess no general method for determining the degree of virulence of a given pathogenic germ for human beings. High virulence for animals is generally regarded as indicating virulence for man; but Koch and Petruschky found that streptococci of high virulence for rabbits did not cause erysipelas in man, and animal-virulent streptococci occur in normal throats. The highly virulent bacilli of bovine tuberculosis seem to have little power of invasiveness in human beings. In pathogenic bacteria, virulence is a variable quantity, changeable at the will o the experimenter. As a general rule, bacteria ar most virulent when taken directly from the animal, and lose virulence, some more rapidly than others, the invasive more rapidly than the toxicogenic, when cultivated on artificial media. Those media best conserve virulence of certain invasive bacteria which approach closest to the natural fluids of the body (blood agar, blood serum). Bacteria commonly gain in virulence by successive passages through susceptible animals. Streptococci, pneumococci, typhoid bac lli, cholera spirilla, etc., may be "trained" in this way into a very high state of virulence, which they lose again more or less gradually on cultivation in the test-tube.

The increase in virulence under these conditions is regarded as the result of survival of the stronger, more resistant elements. At the same time as this selection of strong, virulent races may be taking place, it is also possible that an actual increase in virulence and resistance to the antibodies develops on the part of the bacteria.

Denys and others have shown that virulent streptococci are not taken up and destroyed by rabbit leukocytes in normal serum. A virulent streptococcus has been defined in consequence (Marchand) as a streptococcus that is more or less insusceptible to phagocytosis. In the case of the pneumococcus, too, the more virulent the strain the greater the insusceptibility to phagocytosis (Rosenow). Some bacteria (staphylococci, streptococci) elaborate substances that are inimical to the leukocytes, but the resistance of virulent streptococci and pneumococci to phagocytosis is probably not wholly explainable as due to

leukotoxic substances, because killed and washed cocci, when virulent, are not taken up by leukocytes in normal serum, and Rosenow and others have shown that virulent pneumococci extracted in salt solution set free a substance or substances—"virulin"—which may unite with non-virulent pneumococci and confer on them resistance to phagocytosis and increased pathogenic powers.

When tubercle bacilli or other germs are injected into animals together with the sterilized exudate produced by infection with the corresponding bacterium, then death follows more rapidly than when the bacteria alone are infected, and with little or no evidence of phagocytosis by polynuclear leukocytes. Injections of the exudates only have no effect. Bail assumes that the exudate contains specific substances called aggressins, that paralyze the phagocytes. It has not been demonstrated, however, that "aggressins" are new and special substances. It is probable that the aggressive action of exudates is due largely to the presence in them of substances derived from the bacteria with which they are produced, and which bind or neutralize the anti-infectious substances of the blood and thus reduce their effectiveness.

The question has been asked, Why should not constituents from the infected body act upon microbes in the same way as bacterial constituents act on the cells of the body, and thus set free from the bacteria various poisons for the cells of the body (bacteriogenic antibodies)? This hypothetical conception, which has been stated very clearly by Welch, helps to explain the marked toxic capacities in the infected body of many bacteria that in artificial cultures give little indication of poison-producing powers, and quickly lose their virulence.

In view of the fact that microbic virulence rises on experimental passage through a series of more or less resistant animals, the further question arises, Why does virulence remain at a comparatively low level in nature? Why are the mortality rates of infectious diseases falling rather than rising? Theobald Smith answers these questions on the basis of certain biological considerations. He points out that many pathogenic microbes are reduced more or less completely to a parasitic life; in order that such species may maintain existence they must adapt themselves to conditions that allow invasion of host after host. If such a microbe cannot avail itself of some mechanism of transmission it is sure to perish sooner or later. Now the more virulent the microbe the more rapid the death of the host, and the less the chance of escape to new hosts. Consequently there is going on in nature a constant elimination of the most virulent pathogenic microbes in favor of those that are better adapted to parasitic conditions. The degree of permanence of any species depends on the perfection of its adaptation to the surrounding conditions. At the same time there is taking place a gradual weeding out of the most susceptible hosts, and consequently a small rise in the average general resistance. The general result of this tendency to advancing parasitism must decline in virulence and in mortality.

THE CHANGES AND REACTIONS OF INFECTIOUS DISEASES

Local Effects of Infectious Agents.—These are essentially necrotic and inflammatory. The latter may assume varying anatomical forms: serous, fibrinous, suppurative, diphtheritic, hemorrhagic, necrotic, and proliferative. Depending on various conditions, the same microorganisms may cause different forms of inflammation. Thus the streptococcus may cause serous, fibrinous, and suppurative inflammations. In animals different regions of the body respond somewhat differently to the same organisms. In guinea-pigs, diphtheria bacilli and diphtheria toxin cause a serous or hemorrhagic inflammation when introduced subcutaneously, but a membranous exudate when placed on the mucous membrane of the vulva or the trachea. Different species also differ in their inflammatory reactions produced by the same cause. There are, however, certain forms of inflammation peculiar to certain microorganisms, as for instance the proliferative inflammations resulting in nodules caused by the tubercle bacillus, the bacillus of glanders, and the organism of syphilis. In this sense miliary tubercles, for instance, are quite specific productions.

The inflammatory changes here discussed are caused by chemical substances of microbic origin. They are not necessarily dependent on the presence of living organisms, because the same changes may be obtained by dead bacteria and the sterile products of bacteria. Prudden and Hodenpyl and others have shown that the injection of dead tubercle bacilli into the circulation gives rise to tubercles. The sterile diphtheria poison gives rise to the same inflammatory changes as the living cultures. Leber demonstrated that bacteria attract leukocytes, and Buchner that all bacteria contain non-specific proteins which, when introduced into warm-blooded animals exert positive chemotaxis on leukocytes and stimulate the flow of lymph. These proteins do not differ qualitatively, and consequently do not explain the qualitative peculiarities in the various inflammatory reactions, which may depend at least in part upon more specific substances produced by or present in the different microörganisms as they multiply in the tissues.

It is accepted that the inflammatory reaction, leading as it does to the concentration of leukocytes and serum about the invading microbes, is a measure of protection against infection. Metchnikoff and his followers placed special—almost exclusive—stress on the importance of the phagocytic activity of leukocytes and other cells. Buchner and others emphasized the role of the microbicidal properties of the fluids. The two views are no longer antagonistic. The phenomena of phagocytosis and of extracellular lysis in many cases take place side by side, and phagocytosis probably does not take place before the germs are modified in some obscure manner by substances in the serum.

Leukocytosis.—The majority of human infections is associated with a more or less well-marked leukocytosis. Uncomplicated typhoid fever, measles, rötheln, malaria, dengue, uncomplicated tuberculosis, except of meninges or other serous surfaces, and some forms of sepsis, constitute

exceptions. Inflammatory or infectious leukocytosis is generally an active leukocytosis, *i. e.*, the increase is chiefly in the polymorphonuclear leukocytes, more particularly in the neutrophile forms. The leukocytosis is called active because the cells concerned are mobile, and it is believed that they make their way into the circulation especially from the marrow, which shows increase in the neutrophile myelocytes, by means of amœboid movements in response to positively chemotactic substances. Leukocytes may be produced also by division of existing leukocytes.

Bacterioproteins were regarded by Buchner and Römer as especially active chemotactically because it was found that they caused leukocytosis when injected into animals. Various substances, not all necessarily of this nature, may induce leukocytosis. In animals infectious leukocytosis is caused by nearly all pathogenic bacteria or their products; it is commonly preceded by a short leukopenia. In man, in whom the infections establish themselves more gradually, this initial leukopenia is not so marked or constant as in animals. By some it is regarded as apparent and due to an unequal distribution of the cells, an unusually large number being held back in the capillaries of the internal organs. As the positively chemotactic substances diffuse more uniformly and in greater quantities, the leukocytes are distributed more equally.

It is believed that leukocytosis in infection is beneficial because of the phagocytic activity of leukocytes with respect to bacteria as well as to cellular detritus of various sorts. The destruction of bacteria which are destroyed by phagocytosis (streptococci, pneumococci) is greater the greater the number of leukocytes present in the same serum. The increase in general resistance by increasing the number of leukocytes by various substances—nucleinic acid, salt solution, broth serum —points to the value of leukocytosis. Mikulicz and others obtained good effects in surgical operations upon the abdominal organs by an artificial peritoneal leukocytosis—"preparing the peritoneum."

Tunnicliff and others have made interesting observations on the phagocytic activity of the leukocytes under different conditions.[1] It has been found that at birth the leukocytes are somewhat less active than in the adult; they grow less and less active during first months of life and then more active, the adult standard for streptococci, pneumococci, and staphylococci being reached about the third year. The phagocytic power of leukocytes is greater than normal, with respect to pneumococci, streptococci, and staphylococci, in pneumonia, scarlet fever and other conditions in which there is acute leukocytosis and the outlook is favorable. In pneumonia and in scarlet fever the destructive powers of the leukocytes for pneumococci and streptococci run parallel with the phagocytic power. In severe cases of pneumonia and scarlet fever the phagocytic and destructive powers of the leukocytes may be lower than normal. In recent exudates the leukocytes are more active as phagocytes for streptococci, pneumococci, and tubercle bacilli than the leukocytes of the corresponding blood. The exact causes of the

[1] For a review of this work see Hektoen, *Jour. Amer. Med. Assoc.*, 1911, lvii, 1579.

increase in the activity of the leukocytes are not known; it has been suggested that in acute diseases, in which there is leukocytosis, the increase in activity is owing to the predominance of young leukocytes.

In certain chronic infections, notably chronic pneumococcus endocarditis and chronic erysipelas, the phagocytic activity of the leukocytes may be either above or below normal; at times there may occur a distinct fall in their phagocytic power, which may be specifically limited to the infecting microörganism or observable only in the native serum or both.

Effects on Red Corpuscles.—Anemia is common in infectious diseases, and it is of interest that toxins capable of laking red corpuscles are produced by several pathogenic bacteria. Van de Velde found that staphylococci produce a lysin of this kind (staphylolysin). This substance seems to be produced by all pathogenic staphylococci. Normal human blood contains an antilysin, and in staphylococcus infection newly formed antilysin develops in large quantities. Ehrlich and Madsen found a lysin in crude tetanus poison (tetanolysin). Besredka studied the lysin of virulent streptococci (streptolysin), the activity of which is indicated in the laking of blood observed after death in "sepsis," and in experimental streptococcus infection. Ewing found in primary hemorrhagic smallpox a hemoglobinemia with pigmentary deposits similar to those seen in puerperal streptococcus septicemia. G. F. Ruediger found that streptolysin has the constitution of a toxin, but as yet no immune antistreptolysin has been produced, though the serum of different normal animals contains distinct antibodies.

Bacteria also produce hemagglutinins (Kraus), and it has been suggested by Flexner that the hyalin thrombi of red cells in typhoid fever are caused by such agglutinins. Necrosis in the liver in hog cholera has been referred to hyalin thrombi by Boxmeyer, and Pearce produced liver necrosis by injecting hemagglutinins. That red corpuscles undergo changes in many infectious diseases is shown also by the extensive phagocytosis of red corpuscles that occurs in the spleen, the lymph nodes, the hemolymph glands, and the lymph and bloodvessels in various parts of the circulatory system in typhoid fever, scarlet fever, and other infectious diseases, and which has been studied by Mallory, and by Warthin with special reference to the hemolymph glands.

Changes in Blood-making Organs.—Enlargement of the spleen is characteristic of many infectious diseases. This may depend in part on the lodgement there of degenerated red corpuscles, disintegration of which occurs on a large scale in certain infections. The phagocytic activity of non-granular leukocytes and endothelial cells is often remarkable. The exact mechanism requires further study, with special reference to substances of the nature of opsonins. Jawein found that intoxications with the chlorates of potassium and sodium and with toluylendiamin caused splenic enlargements in correspondence with the destruction of the red cells which were taken up by the cells in the splenic pulp which enlarge and multiply at the same time as hyperemia develops. Splenic enlargement may also be dependent on an active hyperplasia connected with the formation of specific protective substances, as in typhoid fever.

In infectious diseases the fatty marrow is frequently replaced by lymphoid, in which the neutrophile myelocyte is the chief element. Phagocytic cells, the action of which is directed chiefly toward red corpuscles and leukocytes, also appear. Myelocytes appear in the spleen and also in the blood. In the lymph and hemolymph nodes, endothelial proliferation and phagocytosis are the most striking changes—and, according to Warthin, the destruction of red cells by phagocytosis may be greater in the hemolymph glands than in the spleen.

Diverse Actions of Microbic Poisons.—The parenchymatous degeneration in infectious diseases is probably caused by microbic poisons, although Litten, Welch, and others claim from experiments that they may result from hyperthermia. Naunyn, however, obtained different results. The exact relations of bacterial substances to the formation of amyloid material are obscure. Focal necrosis occurs in lymph glands, spleen, bone-marrow, and parenchymatous organs in many infectious diseases, due to action on local cell areas.

Many infectious microbes and their poisons show a special affinity for the nervous system. The tetanospasmin unites with constituents in the neurocytes, which it reaches by way of the axons (Meyer and Ransome). Lepra bacilli have a selective affinity for nervous tissue. The constituent of the crude diphtheria toxin that Ehrlich called toxon, causes paralysis in rabbits quite like that of peripheral neuritis. Grave changes in the spinal cord may develop in different infections.

The investigation of the influence of microbic poisons on the functions of the various glands and on the nerves of the circulatory apparatus is as yet in its beginning. The extract of the adrenals of guinea-pigs and rabbits that have died of diphtheria intoxication and other infections has no power to raise the blood pressure. Paessler and Romberg conclude that in experimental pneumococcus, pyocyaneus, and diphtheria infections, vasomotor paralysis is the real cause of the failure of the circulation. Typhoid infection lowers the blood pressure, while staphylococci, streptococci, and colon bacilli cause it to rise. The toxicity of the urine has been claimed to be greatly increased in infections, but uniform results have not been obtained.

Fever.—While its course varies greatly in different infections there seems no doubt that the presence in the body of active infectious material, as a rule, causes fever. The introduction under the skin of a small amount of dead bacteria, as in protective inoculations, is often followed by a distinct though slight febrile reaction, caused by the splitting of bacterial substances.

Numerous experiments have been made to isolate the fever-producing substance in bacteria, but the recent experiments of Vaughan and of Friedberger show that the breaking up of any foreign protein introduced into the blood and tissues of the body may be associated with fever, and furthermore that different types of fever—continuous, intermittent—may be produced at will by the varying of the quantities of the protein, *e. g.*, egg white, and frequency with which it is introduced. In other words, experimental animal fever may be made to describe the same cycles as fever in man. When excessive quantities

of protein are introduced collapse with subnormal temperature may result.

For centuries fever was regarded as the expression of an effort on the part of the body to overcome the cause of the fever. Liebermeister was the first to break with this conception and to hold that the pyrexia of fever is in itself harmful. In view of the recent experiments on fever the pyrexia may be taken as an indication that foreign protein is being broken down and as a concomitant of the activity of the protective and anti-infectious mechanisms. Whether the rise of temperature *per se* has any effect, deleterious or beneficial, on the course of the infection is not settled.

Effects on Metabolism.—Microbic infection may alter the chemical composition and metabolic processes of the body, either directly, by setting up destructive changes in the tissues and body fluids, or indirectly, by lowering functional activity. The best understood of the direct destructive changes are the fermentative and putrefactive processes of the gastro-intestinal tract. The lowered acidity of the gastric juice, the atony and lessened peristalsis which accompany certain infections, favor the growth of yeasts and bacteria in the gastro-intestinal contents. Fortunately many of the resulting products so irritate the mucosa that vomiting and diarrhœa take place. Absorption, however, is usually sufficient to bring about important changes in the body fluids. A few of the products, such as cholin and neurin are extremely toxic. Most of the products, however, have but slight toxicity and are readily disposed of by the body. Such substances as cadaverin and putrescin are excreted unchanged. Most of the acids unite with the alkalies of the body fluids to form salts, which may appear unchanged in the urine. Such substances as phenol, cresol, and certain aromatic oxyacids unite directly with $KHSO_4$, glycocoll and glycuronic acid, to form non-toxic conjugation products, which are excreted in the urine unchanged. Others, as indol and skatol, are first partially oxidized and then form conjugation products. Still others, as tyrosin, are completely oxidized in the tissues. Some of these products are readily detected in the urine, and are therefore of diagnostic importance.

Pathogenic microörganisms, either alone or in association with non-pathogenic forms, set up similar destructive changes in the tissues themselves. These are illustrated by the disintegration of erythrocytes in malarial fever, the necrosis and liquefaction of abscesses, and the putrefaction of gangrene. The agents bringing about these changes are: the toxins and enzymes secreted by invading microörganisms, the enzymes of leukocytes and red blood corpuscles, and the autolytic processes of the fixed cells. The resulting products vary from the simple albumoses and peptones of autolysis to end-products similar to those of intestinal putrefaction. Certain of these substances, such as hemoglobin, histon, Bence-Jones albumose, and certain diazo-bodies, may appear in the urine, and are of diagnostic importance.

Apart from these directly destructive tissue changes, infection may bring about important alterations by stimulating katabolism. This stimulation may be due either to a direct action of the infectious agents

or their toxins on the tissues, or indirectly to nervous, circulatory, and respiratory changes. The increased katabolism manifests itself by increased heat-production, and by the appearance in the urine of increased amounts of all of the metabolic end-products. Nitrogenous excretion, for example, may be increased by this means two or three times that of normal. Infections may also bring about important changes by causing abnormal losses and retentions. Such losses may be illustrated by albuminuria, diarrhœa, and hemoptysis, the discharge of inflammatory exudates, and the sloughing of necrotic tissues; the retentions by anuria and catarrhal jaundice. The resulting tissue changes are mainly quantitative in character; but important qualitative changes may follow secondarily.

The best understood of the indirect metabolic changes due to altered functional activity are those resulting from a reduction in food intake. This may be brought about by anorexia, pain, muscular inability and lack of nervous control, by vomiting, diarrhœa, and diminished power of digestive fluids. The resulting metabolic changes approximate those of inanition. There is a rapid and ultimately an almost complete consumption of the body fats and carbohydrates, followed by a rapid consumption of the body proteins. The respiratory coefficient decreases from 0.85, its value on an ordinary mixed diet, to approximately 0.7, its value on a pure protein diet. The nitrogen of the urine rapidly drops to a minimum, which represents the smallest protein destruction compatible with life, and remains at this low level as long as the body is living on its stored-up fats and carbohydrates. As soon as the body begins to draw upon its protein as its main source of energy, there is a rapid increase in the urinary nitrogen. Since practically all the sodium chloride of the food usually appears promptly in the urine, on withdrawing food the sodium chloride excretion rapidly decreases to a small amount, representing only that set free by tissue destruction. The food usually contains an excess of sodium over potassium, while the tissues contain an excess of potassium salts. On withdrawing food, therefore, the K-Na ratio in the urine changes from 2 to 3, the ratio on an ordinary mixed diet, to approximately 3 to 1, the ratio of the salts in the living tissues.

The metabolic processes may also be altered by a reduction in the oxygen supply. This may be brought about by such factors as narrowing of the respiratory passages, reduced respiratory movements, reduced alveolar surface, and reduced oxygen-carrying capacity of the blood. The exact nature of the resulting metabolic changes are poorly understood; but there is usually an increase in the urine of oxalic acid, lactic acid, ammonium salts, xanthic bases, and other products of incomplete oxidation. Marked alterations may also follow the destruction or perverted activity of important metabolic tissues. The exact nature of these changes is as yet largely a matter of conjecture.

It is probable also that there are profound changes in delicate protein molecules due to changes in temperature alone. When we consider the marked changes in the ionization of simple salts, and in the arrangement of atomic groups in simple organic compounds, that follow an increase

of only a few degrees in temperature, it is clear that there must be innumerable similar changes in tissue molecules due to the same cause. What these changes are is yet a matter of hypothesis. Theoretically one would expect an increased dissociation of complex substances, a rearrangement of simpler radicals, and a hastening of all processes depending on ionization. The fever, therefore, would tend to increase in the body the formation of end-products of tissue metabolism.

Considering the chemical processes of infectious diseases as a whole, one is struck by the prominent role played in these diseases by the products of protein decomposition. One sees how much the medicine of the future depends on an increase in knowledge of these products. When one considers that, in many diseases, the harmful effects are due as much to the action of these substances as to the direct action of the microbes themselves, the possibility of assisting the organism, in some direct manner, to neutralize these products, or to inhibit the action of the enzymes that gives rise to them, is suggested.

The Formation of Antibodies.—Most important reactions in infections are those that result in the formation of antibodies, the general action of which is to destroy the invading microbes and to neutralize toxins. For centuries it has been a matter of common knowledge that recovery from an infectious disease leaves behind a more or less well-marked immunity to that disease, and this we now know is intimately associated with these cellular reactions. Our knowledge of immunity—natural and acquired—and of the reactions whereby antisubstances are produced, is inseparably connected with that of modern protective and therapeutic inoculation and serum therapy.

IMMUNITY, ANTIBODIES, SERUM THERAPY, AND SPECIFIC INOCULATIONS[1]

Introduction.—The development of immunity is the usual and natural termination of many acute infectious diseases. Advantage was taken of this fact in the inoculation of smallpox and later the success of vaccination suggested that possibly infection with attenuated virus in general would give the same protection as with the fully virulent. In 1881 Pasteur successfully vaccinated sheep against anthrax by means of cultures of attenuated anthrax bacilli, and the principle of artificial immunization (vaccination, protective inoculation) against diseases of known microbic cause was established.

The beginning of the study of the finer mechanism of infectious reactions may be placed in 1888, when Roux and Yersin discovered diphtheria toxin. Then came Behring's discovery, in 1890, of diphtheria antitoxin in the body of animals injected with increasing quantities of diphtheria toxin, and analogous observations with respect to tetanus toxin (Behring and Kitasato), and to the vegetable toxins, ricin and abrin (Ehrlich). Behring showed further that antitoxic serum may

[1] In revising this part the writer made free use of materials prepared by him for various lectures on immunity and allied subjects.

protect healthy animals against fatal doses of the corresponding toxin, and even cure those already sick. "Thus an innate faculty of the animal organism to develop in a marvellous manner its own resources was turned to the common good"—curative serum therapy was established.

The expectation that it would be an easy matter to obtain specific sera against all microbic diseases proved illusory because many infectious microbes do not produce diffusible toxins as do tetanus and diphtheria germs. It became established that *acquired antitoxic immunity*, which depends on the neutralization of toxin by specific antitoxin, has only a limited range. Many cases of natural immunity to toxins appear to be due to an insusceptibility of the cells of the animals to the toxin, which may, as shown by Metchnikoff in the case of tetanus antitoxin, circulate free in the blood of the immune animals. In other cases immunity may be the result of absorption of the toxin by cells of relatively little importance to the economy, or on which the toxin has little pathogenic power. The chicken has a relatively high immunity to tetanus; it requires 200,000 times more toxin, gram for gram of weight, to kill a chicken than it does a horse; yet chickens contain no tetanus antitoxin.

In many microbes the pathogenic poisons are regarded as intimately bound up with microbic cells. While it is possible that special poisons are elaborated and set free under the stimulus of the infected body, the current view is that poisons are liberated as the microbic cells disintegrate or result from the breaking down of the microbic proteins. At all events, these poisons are not true toxins in the immunological sense because they do not appear to induce the formation of specific antitoxins. As active immunity is established against microbes of this class, new and specific substances different from antitoxins accumulate in the blood and other fluids of the body. These substances cause the solution of the microbes either by direct action or lysis (lysins), or by so changing the microbes that they are subject to phagocytosis (opsonins). As the action in this instance is directed against the microbes themselves rather than against their secretory products, this form of immunity is spoken of as anti-infectious or antimicrobic to distinguish it from the antitoxic. Acquired antimicrobic immunity would seem to depend on rapid and complete destruction of the microbes so that only small doses of poison, however evolved, are set free; it seems likely also that the poisons themselves may be rapidly reduced to non-toxic products. Of the immune serums of the anti-infectious type the most successful is the antimeningitis serum which appears to destroy meningococci directly, as well as to cause increased phagocytosis and endophagocytic destruction, and to destroy poisonous substances.

In acquired immunity we distinguish between the active and passive forms. The *passive* form results from the introduction of ready-made antisubstances as in the injection of antidiphtheria serum, while the *active* form develops from reactions within the body produced by infectious germs and other substances that have the power to incite the production of antisubstances.

The Explanation of the Origin of Antitoxins and Other Antibodies.—The modern study of immunity has been directed by Ehrlich's lateral chain

or receptor hypothesis. First advanced to explain the origin and action of diphtheria antitoxin, and to give a basis for its standardization, the hypothesis proved applicable to a widening range of similar problems.

Bacterial and other toxins, when introduced in suitable animals, have the power to cause the formation of specific antibodies. All substances having this property are called antigens. Now, Ehrlich's conception of the action of antigens is illustrated well by his explanation of the way in which diphtheria toxin is supposed to act. Briefly stated, Ehrlich assumes that a toxin can be harmful only after a union with constituents (side-chains, receptors) in the protein molecules of the cell of proper stereochemical configuration ("as a key fits its lock"), somewhat in the same way as food particles are taken up. If a cell contains no receptors with which a toxin can unite, then that cell is immune to the toxin. The red corpuscles of the newly hatched chick are quite insusceptible to spider toxin (arachnolysin), which they do not take up; later, however, cells appear with the proper side-chains or receptors, and now the toxin causes laking (Sacks). In some animals immune to certain toxins, the latter may remain free and seemingly unchanged for days and weeks. That toxins unite firmly with cells is shown by the firm fixation of tetanus toxin by the nerve tissue (Wassermann and Takaki). Dönitz has demonstrated that it concerns here the gray matter, the neurocytes.

Like complex compounds of known composition, the toxin molecule is regarded as having two distinct atomic groups, one whereby it unites with cell side-chains or receptors, and called the haptophore or binding group, and one by means of which it exercises its peculiar toxic effect, and hence called the toxophore group. This conception explains the fact that when toxin becomes old, or is subjected to chemical and other influences, it may weaken in its special toxic or other properties, but nevertheless produce antitoxin in suitable animals. Evidently the functional group is the more sensitive, whereas the haptophore group persists and unites with cell receptors. Toxin so changed is called toxoid. It is possible to separate in point of time the action of the two groups: In frogs tetanus toxin is not toxic below 20° C. in spite of the fact that the toxin is bound to nerve cells below this temperature; only at a higher degree does the toxophore group become active (Morgenroth).

Now when certain receptors of a cell are occupied by the haptophore groups of an antigen to such an extent that it interferes with their function in metabolism, then a regeneration of receptors begins, which, according to Weigert's law of regenerative overcompensation, gives rise to more receptors than the cell needs, and these are thrown off from the cells into the circulation. Hence, any cell that binds antigen and reproduces receptors produces antisubstances which are simply free receptors.

Antitoxins, antiferments, agglutinins, opsonins, precipitins, and various amboceptors are conceived as free receptors, the nature and function of the particular receptor depending on the antigen that by union with cell receptors stimulated the mechanism of receptor formation. Antigens are protein substances and many proteins that are foreign to an animal exercise antigenic powers if introduced into its

blood or tissues. Some of the principal facts about antibodies, the laws governing their formation, their modes of action, etc., now follow.

The Formation of Antibodies under Various Conditions.—By measurement of antibodies as they appear in the blood after the introduction of antigens, much has been learned of the manner of antibody formation, and the most important facts bearing on this point are shown in the antibody curve. The simplest curve, that obtained after one injection of antigen in a normal animal, shows that for two or three or four days there is, as a rule, either no change or there may be a fall in the specific antibody if such is already present. At the end of this period of latency new antibody appears. This increases until an acme is reached, which in most cases seems to be about the tenth or twelfth day; before long begins the last phase of the curve, namely, a gradual return to normal, which may last only a few days or several weeks, and even much longer.

Animals, including man, normally carry in the blood small amounts of a large number of antibodies, which possess specific affinities for antigenic substances, and which probably do not differ much from the corresponding bodies that arise on immunization. In favor of this is the fact that the primary fall in antibody in the blood on immunization is specific, that is, affects only the antibodies for the particular antigen injected. This fall, which occurs also on reinjection in previously immunized animals, is regarded as the result of neutralization of the existing antibodies, although the amount of antigen introduced often seems too small to cause the fall in this way.

The height and duration of the simple curve vary depending on the kind and amount of antigen as well as on the place of introduction, and also, of course, on the individual animal. It is important to note that the yield of antibodies does not increase in the same ratio as the antigen is increased. Small amounts of bacteria and other antigens may cause more antibody to form on intravenous than on subcutaneous injection. In animals previously acted on by an antigen, the antibody mechanism may be especially sensitive to that antigen, and respond more promptly and fully than in the fresh animal. In this way is explained the quick rise of opsonin, often seen on therapeutic injections of vaccines in chronic infectious conditions, as well as other phenomena of allergy, which will be discussed a little later.

When many injections of antigen are given at intervals more or less variations of the simple curve result. It is the rule in immunization with toxins and bacteria to begin with small quantities and to reinject with increasing quantities, carefully graded to avoid severe reactions, at intervals of a few days for a considerable period. A continued and more or less cumulative production of antibodies may be induced also by daily injections of small and constant doses of antigen. In some cases, however, it seems difficult to secure marked cumulative effects. Animals under the continuous influence of antigens eventually lose the power to produce antibodies, to regain it, if at all, only after periods of rest.

A cellular antigen, like microbes or other cells, may give rise to lysin, agglutinin, opsonin, and other antibodies at the same time. In some

cases these different antibodies appear to describe parallel curves; in other cases, there is no such parallelism which would seem to indicate that we are dealing with distinct substances.

When several antigens are introduced at the same time, as occurs in secondary and multiple infection, the amount of antibody produced for a particular antigen probably is less than when that antigen alone is introduced. Secondary infections in typhoid fever, such as pneumonia, depress the agglutinin curve. In dogs pneumonic infection (distemper?) may suspend almost completely the production of antibodies for foreign corpuscles. It is possible that the streptococcus and other infections of eruptive diseases, notably smallpox and scarlet fever, and of tuberculosis, may depend in a measure on the inability of the body to respond freely to the stimulus of more than one antigen at a time; and the aggravation of the primary disease, as secondary infection sets in, may be due to depression in the production of antibodies for the primary disease, as illustrated by the suspension of the tuberculin reaction by an attack of measles. Here we may assume with v. Pirquet that the measles antigen suspends the formation of the bodies that cause the tuberculin reaction.

In his classical experiments on immunity through inheritance and nursing, Ehrlich showed that certain antitoxins pass over into the milk, and since then antibodies have been found to occur also in transudates and other fluids. Normal antibodies are more concentrated in the blood than in the lymph; traces only occur in the cerebrospinal and pericardial fluids and aqueous humor. So far as the blood and lymph are concerned, the changes in concentration during active immunization of dogs with foreign blood run practically parallel, the concentration in the lymph being always somewhat lower than in the blood. In dogs transfused with blood of dogs actively immunized, the antibodies rapidly reach the same relative concentration as in normal and actively immune animals. In inflammatory exudates the antibody concentration may approximate that of the blood.

Where Are Antibodies Formed?—It has been found that after injection of antigens, the spleen, bone-marrow, and lymph nodes show increase of antibodies before the blood which, however, soon gains more and more while the tissues mentioned gain relatively less. The most natural conclusion would seem to be that the antibodies are formed in the blood-making organs, and the results of splenectomy certainly favor this view, as it is followed by a lower but typical curve if made shortly before or shortly after the injection of the antigen. Experiments also show that the spleen binds antigen; the injection of splenic pulp from an animal injected with antigen into a fresh animal gives new antibody formation. Loss of blood increases the output of antibodies, and this also points to the blood-making organs as their source.

It is claimed that antibodies are produced by tissues at whatever place the antigen is introduced, but there is no convincing experimental evidence of this. No matter how or where antigen is introduced, antibodies appear in the blood, whence they rapidly make their way into lymph and other fluids, and it is consequently impossible to learn

whether antibodies in an exudate are produced by the adjacent tissue. Whether antibodies are produced in the blood itself by leukocytes is also under discussion. If they are formed by and in the blood, it would be reasonable to seek them in animals freely transfused with the blood of animals given an optimum dose of antigen a short time before, but in experiments of this kind on dogs no antibody formed in the transfused animals, the antigen very quickly being fixed by tissues or removed from the blood in some way, the blood seemingly taking no direct part in actual manufacture of antibodies.

The Antibodies in Disease.—In acute bacterial diseases the course of the antibodies that develop in the acute attack resembles altogether that of the antibody curve after a single injection of antigen in a normal animal. This holds good for pneumonia, for erysipelas, for diphtheria, for cholera, for the streptococcus opsonin in scarlet fever, etc. These curves show certain definite relations to the clinical phenomena. During the early stages there is a more or less distinct fall in the antibody; as the symptoms begin to subside the curve rises and usually reaches the highest point a day or two after the acme of the symptoms. This curve is readily affected by complications, at the onset of which it usually falls, and in rapidly fatal cases the curve may not return, but sink lower and lower (pneumonia, cholera).

A somewhat different type of curve is given by typhoid fever, at least so far as the agglutinin is concerned, which in most cases appears in the first or the early part of the second week, and usually reaches the height in the third week. In the long latency and late acme of the curve one is reminded more of the curve in animals receiving daily injections than of the curve after a single injection of antigen.

That the content of the blood in antibodies may be increased in chronic infections is indicated very clearly by the power of the serum in syphilis, in gonococcal infections, and in other diseases also, to cause fixation of complement. The allergic reactions, *i. e.*, the special reaction of the infected body to reintroduction of the substances causing the infection, and familiar to all in the form of the tuberculin reaction, are obtainable in an increasing number of chronic infectious processes; according to the current view as to their nature, these reactions also depend on the action of new antibodies. Whether the failure of the tuberculin reaction in late stages and generalized forms of tuberculosis is due to a lack of these bodies is not known, but seems likely. The estimations of the opsonic index show that in chronic infections, notably tuberculosis, the opsonin often seems to fall below normal, being, however, subject to fluctuations of such wide range as to be of diagnostic significance.

The Specificity of Antigen-antibody Reactions.—The word "specific" designates a characteristic of the phenomena of immunity that is of fundamental importance. It has been found that a given antibody has a very special affinity for the antigen calling it forth, so that its action, whatever that may be, is obtained in the most pronounced degree with that antigen, there being, as a rule, but little or at least less affinity for similar antigens of different species. This, in the briefest and most

general sense, is what specific indicates in immunology, and practically all antibody-antigen reactions, both those that occur in the body and those that are observable in the test-tube, follow this law of specific action. It is true that when certain antibodies are richly developed the action may extend to the corresponding antigens from species more or less closely related to that from which is obtained the immunizing antigen, but nearly always in a much less intense degree than in case of the latter. The specificity of antibody-antigen reactions is dependent on the structure of the protein substances concerned; and it means that there are differences in the structure of similar proteins of different origin, that proteins of different species in most cases are not alike. It is interesting that certain animal proteins appear to have no specific relations to species. The most striking example of this kind, in fact the only example that is really well substantiated, is furnished by the crystalline lens: the proteins of the lens of one species is not distinguishable from those of other species either by means of the precipitin or the anaphylactic reaction, as positive reactions are obtainable under the same conditions with lens proteins of widely separated species and even with the lens of the species from which we obtain the immune serum or the sensitized animal. In this case the specificity depends on organ and not species. Whether other proteins, such as those of the sexual cells and of tumors, possess a similar organ-specificness is not determined.

It is the limitation of antibody action by species that gives diagnostic value to the serum reactions in infectious diseases. It is by virtue of this circumstance that agglutination of typhoid bacilli by the serum, in proper dilution, of a patient means typhoid infection; that the reaction to tuberculin means tuberculosis and to gonococci, gonococcal infection; and that the fixation of complement by the antibody-antigen compound has diagnostic significance. The action of antitoxic and other therapeutic serums is strictly specific in this sense. If we wish to prevent any infectious disease by means of inoculation or vaccination we are forced by this law of specific action to inject the bacteria or virus, properly prepared, causing the particular infection we wish to prevent. This aspect of the specificness of infectious diseases was expressed clearly and forcibly by Fuller in 1780, when he wrote: "The pestilence [chickenpox] can never breed smallpox, nor the smallpox the measles, nor they the crystal or chickenpox, any more than a hen can breed a duck, a wolf a sheep, or a thistle figs, and *therefore one sort cannot be preservative against any other sort,*" and, one may add, in reference to inoculation or vaccine treatment, that generally speaking one sort cannot be curative of another sort. If we wish to increase the antibodies against gonococci in the hope thereby favorably to influence a chronic or subacute gonococcal process, we must inject gonococci, and it seems that in view of possible differences in strains, we may do best if we can inject gonococci from cultures of the very strain causing the infection we wish to treat. In all therapeutic inoculation we must inject the bacteria causing the particular infection we wish to overcome; hence exact diagnosis, in many cases possible only by isolation of the infecting germ, is an absolute prerequisite for successful inoculation.

Antitoxins.—Like antisubstances in general, many antitoxins occur in normal animals. Diphtheria antitoxin occurs in small quantities in about 50 per cent. of human beings and in about 30 per cent. of horses. We know very little about antitoxins except from their specific actions. They are found in the fluids of the body, especially the blood. They are changed by heating to 60° to 70° C. and by exposure to light; when dried they tolerate higher degrees of heat and may be kept for a long time. By fractional salting out of proteins it is found that euglobin or pseudoglobulin contains all the antitoxin, the kind of globulin concerned depending on the kind of animal and the kind of toxin used for immunization. At present neutralization of toxin by antitoxin is regarded as the result of union into a harmless substance. The study of this problem was greatly furthered when Ehrlich selected for this purpose toxins the action of which may be followed *in vitro*. In this way the difficulties of the use of living animals were circumvented. The effects of blood-laking toxins (hemolysin like tetanolysin, etc.) and their antitoxins, as well as of certain ferments that give rise to antiferments, are easily followed in the test-tube. In experiments with hemolysins and anti-hemolysins, red corpuscles, freed from all serum, are used as indicators of the effects of various mixtures, the laking being measured by means of simple colorimetric scales. The results of these experiments show that toxic and antitoxic action may take place without the immediate co-operation of the living organism, and that the rapidity with which toxin and antitoxin unite depends on the degree of concentration, temperature, medium, amount of salts present, etc. In several instances it has been shown that they obey the laws of multiple proportions. The same general laws appear to govern the union of other antisubstances with the substances upon which they act.

Recent union between toxin and cells may be broken up by antitoxin. This is shown in Madsen's experiment of "healing in the test-tube," in which antitetanolysin was found to prevent laking of corpuscles by tetanolysin even after the latter had become united with the corpuscles. In this way may be explained the good effect of antitoxin in large doses after characteristic symptoms have developed. As time goes on, however, the union between toxin and cell becomes firmer and firmer, and the antitoxin soon loses the power to separate the toxin from the cell—*i. e.*, to arrest the toxic action. This shows the necessity of early administration of antitoxin in large doses in diseases like diphtheria and tetanus—lessons taught also by clinical experience.

The sera of immunized animals do not possess the same curative and protective value. Depending on various complicated factors, such as constitution of the animal, duration and degree of immunization, etc., the potency of antisera varies within wide limits. Hence it becomes necessary to establish units for measurements of the strength of sera. Progress in serum therapy depends on the employment of sera of ascertained quality, so that comparable results may be secured. In this country antidiphtheric and antitetanus sera are official, and given quantities must contain definite numbers of antitoxic units.

Ehrlich demonstrated that there is no fixed relation between the

toxicity of diphtheria toxin, as represented by the soluble products of diphtheria bacilli in broth cultures, and its power to combine with diphtheria antitoxin. Various influences—time, heat, light, etc.—reduce its toxicity without altering its power to combine with antitoxin. Thus it became necessary to establish an arbitrary standard of antitoxin, which is more stable than toxin, by comparison with which other antitoxic serums might be standardized. An accurately tested serum was carefully dried for preservation and is now used as a standard. As the antitoxin unit or immunity unit, Ehrlich established that quantity of antitoxic serum that will neutralize 100 lethal doses (M L D) for guinea-pigs weighing 250 grams. Two important limits are established, namely, (1) L°, by which is meant the amount of toxin that exactly neutralizes one immunity unit of antitoxin, and (2) L+, by which is meant the amount of toxin that will neutralize one unit of antitoxin + the amount necessary to kill a guinea-pig, weighing 250 grams, in four days. Ehrlich showed that when the L° quantity of toxin is partially neutralized by adding fractional amounts of antitoxin, there is at first no decrease of toxicity in the mixtures, as there should be if the true toxin were bound by antitoxin. Evidently the crude diphtheria poison contains certain substances that are non-toxic at the same time as they bind the antitoxin with greater avidity than the toxin proper. The body which has the greatest affinity for antitoxin is called *prototoxoid*. It may require as much as one-fourth of the immunity unit to saturate the prototoxoids in the L° dose of poison. From now on the toxin diminishes in toxicity in exact proportion to the amount of antitoxin added. When, say, two additional fourths of the antitoxic unit have been added to L° of toxin, the mixtures no longer produce acute death, but local œdema and late paralysis, and this is accounted for by Ehrlich as due to another toxic body with less affinity for antitoxin than toxin and prototoxoid, and designated as *toxone*. The difference between toxoid and prototoxoid is this, that the latter has a stronger avidity for antitoxin, while toxoid in this respect equals toxin proper. Both toxoid and prototoxoid are without active toxophore groups. Ehrlich's explanation of the fact that a certain amount of antitoxin may be added to the crude diphtheria poison without lessening its toxicity has been accepted generally. His belief, however, that the poison contains two active toxins—namely, the diphtheria toxin proper and toxone—has been attacked by Arrhenius and Madsen, who regard the reactions between toxin and antitoxin as reversible, analogous to the reactions between other substances of feeble affinity, and consequently obeying the Guldberg-Waage law of mass action. They have calculated the constant K for a number of combinations. It has been pointed out, however, that the mixtures are not homogeneous, and that the degree of reversibility, if any really exists, is extremely small; and at present the Ehrlich interpretation of toxin and toxone seems to have the greater number of followers.

Lysins (Amboceptors and Complements).—Lysis, or the solution of cells, microbic and otherwise, by serum, is a complex process. Nuttall first brought proof that blood and other fluids are bactericidal. Buchner regarded the bactericidal substances of blood as the principal protective

agents against infection, and for this reason he named them alexins ($\alpha\lambda\epsilon\xi\epsilon\iota\nu$ = to guard). R. Pfeiffer observed that cholera germs placed in the peritoneal cavity of a guinea-pig, immunized to cholera, undergo lysis—"Pfeiffer's phenomenon." Before long similar phenomena were observed with respect to typhoid, pest, and other bacteria. Pfeiffer showed, further, that lysis occurs also when cholera germs are placed in the body of a normal guinea-pig provided they are mixed with the serum of an immune animal. As the unit of immune cholera serum, Pfeiffer designates that amount that saves a guinea-pig weighing 200 grams from ten times the fatal dose of an eighteen to twenty-four hour old agar culture of cholera bacteria mixed with the serum, the total quantity of the mixture always being 1 cc. "Pfeiffer's antibodies," as the active substances in the immune serum were called, were found to be strictly specific; at first he believed that his antibodies could be activated only by something in the body of living animals; but Metchnikoff and Bordet demonstrated that the destruction takes place *in vitro* also, when normal serum is added to immune serum.

The study of bacteriolysis benefited greatly from the discovery by Bordet that repeated injections of an animal with the red corpuscles of another species gives rise in the blood of injected animals to a specific substance that *in vitro* lakes these corpuscles in the same way as bacteriolytic serum causes lysis of bacteria. This was studied thoroughly by Ehrlich and his co-workers. The serum of normal animals and of man contains several lytic substances, and by immunization with animal cells and microbes, as well as their disintegration products, the amount of lysin may be increased in a specific manner.

Baumgarten and others have urged that the lytic and destructive action of normal and immune serum is due to purely physical factors, especially osmotic disturbances, and, in the case of bacteria, to a lack of assimilable food substances. But this view has had to give way in favor of more specific action. Nor has it been possible to explain lysis as due to alkalinity, which, however, may play some role in the process. Serum causes lysis by virtue of two distinct interacting substances, one, as a rule, destroyed by heating at 55° C. for thirty minutes, the complement, and one that is more thermostable (Bordet). Serum that has lost its lytic power by destruction of the complement by heat or otherwise is said to be inactivated; it may be reactivated by the addition of fresh serum containing the suitable complement. The thermostable body, commonly called immune substance or amboceptor, is the one that is produced in a specific manner during immunization. Amboceptors are assumed by Ehrlich's hypothesis to be free cell receptors, which differ from antitoxins in having two haptophore groups, one by which they unite with the receptors of the corresponding bacterial or other cells—the cytophile group—and one by which they unite with the thermolabile complement —the complementophile group. In itself the amboceptor is without any destructive action.

Amboceptors are fairly stable bodies; heating to 60° C. for twenty hours has no marked effect upon them, but heating to 70° C. for one hour destroys them. They are non-dialyzable and may be kept for

years. Manwaring has shown that in serum heated sufficiently to destroy the complement only, it is possible to demonstrate the presence of substances that on the one hand favor and on the other hand inhibit hemolysis. These substances prevent the determination of the physicochemical laws of the union of amboceptors with corpuscles.

The same serum may contain several amboceptors, and the amboceptors in different serums differ as a rule. Amboceptors capable of uniting with the same cell, bacterial or otherwise, may differ in two respects—namely, in their cytophile and in their complementophile groups. The same amboceptor may be able to unite with several complements by virtue, one might say, of possessing several complementophile groups (polyceptor). A serum may contain amboceptors for a certain cell but not any suitable complement, as in the case of dog blood, for instance, which contains an amboceptor readily taken up by anthrax bacilli; the complement necessary to complete the lysis may be found, however, in some other animal, *e. g.*, the rabbit. The researches of Flexner and Noguchi have shown that cobra and other venoms play the part of amboceptors in hemolysis, and Kyes showed that lecithin may act as complement to the venom amboceptors.

Complement.—The complements are sensitive ferment-like substances normally present in blood. It is claimed that they are not increased, at least not specifically, by immunization with foreign protein, but this may not be accepted as final. Complements in general are sensitive to heat and other influences and are neutralized by dilute solutions of various salts. On dialysis complement appears to separate into two parts, one seemingly going down with the globulin precipitate, the other remaining in solution, full complement action being restored on the reunion of these elements in salt solution. It is claimed by some that the complement remains in the albumin portion, being in reality rendered inactive by excess of alkali.[1]

When complement is attached to red corpuscles, microbes, or protein molecules by means of the proper amboceptor lysis and protein splitting result. It seems as if it concerns the action of ferments that produce their effects by contact. According to Bordet's view the amboceptor modifies the cells in some way so that they are affected by the complement which, however, does not unite with the amboceptor.

Abderhalden claims that when foreign substances are introduced into the body directly without first being digested, the blood plasma acquires new fermentative powers, proteolytic and peptolytic as well as glycolytic and lipolytic. He calls these ferments protective ferments; their action is not so narrowly specific as that of the substances concerned in the ordinary reactions of immunity. In pregnancy the blood contains a ferment that digests placental proteins.[2]

[1] Noguchi and Bronfenbrenner *Jour. Exper. Med.*, 1911, xiii, p. 78.

[2] Abderhalden: *Die Schutzfermente des tierischen Organismus*, Berlin, 1912. See also Jobling: "Studies on Ferment Action," *Jour. Exper. Med.*, 1912, xviii; and Dick: "On the Nature of Proteolytic Substances in the Blood," *Jour. Infect. Dis.*, 1911, ix, 282; and "On the Development of Proteolytic Ferments in the Blood during Pneumonia," *Jour. Infect. Dis.*, 1912, x, 383.

Complement Fixation.—Bordet and Gengou showed that as antibody and antigen come together complement is fixed or absorbed. This reaction is now used to identify foreign proteins of microbic and other origin as well as specific immune substances. When antigen, antibody, and free complement are mixed under proper conditions, the complement soon becomes fixed so that no laking occurs when red corpuscles and specific amboceptor are added; if antigen or antibody is absent the complement remains free and laking results. Wassermann's test for syphilis, once regarded as a typical example of complement fixation, is now known to depend on a different mechanism (Noguchi, Peritz). Complement fixation has been found useful in gonococcus infections, glanders, anthrax; in the study of antibodies in therapeutic sera; and also for the demonstration of bacteria and protein substances under various conditions.

Opsonins and Phagocytosis.—Metchnikoff established the general occurrence of phagocytosis in health and disease; Denys and others showed that the fluids of the body are necessary for phagocytosis as they make bacteria susceptible to phagocytic action; and we now know that this property of the body fluids is due to definite substances of the nature of antibodies, called opsonins by Wright, which attach themselves to microbes and other cells and so alter them that they are taken up by the phagocytes. In some cases it is easy to demonstrate by laboratory methods that bacteria so ingested are destroyed within the phagocytes, whereas they grow freely in suspensions of phagocytes without the presence of opsonin, and in opsonic serum alone. Recent investigations have served to establish more clearly and firmly the great importance of phagocytosis in many infections, notably with streptococci, pneumococci, tubercle bacilli, and other bacteria that are not destroyed readily by lysis, and that even in the case of bacteria subject to lysis phagocytosis plays a larger role than first believed. At first opsonins were regarded as simple bodies, but it was soon found that two substances were involved, one easily destroyed by heat and not increased by means of antigens, the other relatively resistant to heat, provided with specific affinities, and produced anew in immunization. The heat-resistant opsonic elements are capable of opsonic action by themselves and unite firmly with the objects acted on, but the opsonic effect is increased very much by means of the thermolabile, complement-like element. Whether opsonification is caused by distinct, independent substances or by antibodies with other actions as well, such as lysins, has been much discussed.

Precipitins.—In 1897 Kraus discovered that the serum of immunized animals may form a precipitate in the sterile filtrates of broth cultures of the corresponding bacterium. This reaction was found to be quite specific. In 1899 Tschistowitsch and Bordet found that serum of an animal injected with alien serum causes precipitates in the alien serum. Wassermann and Schütze, and Uhlenhuth applied the reaction to the differential diagnosis of human and animal blood and albumins, and the precipitation method or test is now established firmly in forensic

medicine. Nuttall[1] has made extensive studies into the biological relationship of animals by means of precipitating sera.

The presence of precipitable substance (precipitinogen) is demonstrated by means of specific immune serum. In man and animals precipitinogen is present in the blood, the organs, in milk, and in various pathological products (inflammatory exudates, transudates, albuminous urine, etc.). Precipitinogen of bacterial origin may be secured by means of filtered extracts with NaCl solution of agar cultures, in filtrates of broth cultures, and of extracts of organs of infected animals (anthrax, black leg). It is quite resistant to heat, decomposition, etc., and numerous efforts have been made to obtain it in pure form, but as yet the results are conflicting. Precipitin is regarded as a complex body composed of two atomic groups, a stable group by which it unites with precipitinogen, and a more labile group by virtue of which precipitation takes place. The functional group is destroyed by heating at 58° to 60° C. in the case of bacterioprecipitin, and at 70° C. in case of milk precipitin (Müller) and albumin precipitin (Eisenberg), and also by standing outside of the body. In a mixture of precipitin and the modified substance (precipitoid) the latter may have the greater affinity for precipitinogen, and bind all that is available without causing any precipitate. When dry, precipitin may be heated to 100° C. for a half-hour without damage; it is destroyed at 130° to 135° C.

When precipitin and precipitinogen, *e. g.*, serum and antiserum, are mixed properly a precipitate develops. The precipitation is more rapid in case of animal precipitin and serum than in case of bacterial filtrates and bacterioprecipitin. In the latter instance the reaction becomes apparent usually after a few hours, first as a cloudiness, then flocculi appear which settle to the bottom as amorphous masses, leaving a clear supernatant fluid. The reaction is furthered by a temperature of 37° C. Neisser and Friedberger have observed that the precipitation that occurs when eosin and bismarck brown are mixed—colloids of opposite electrical charge—presents certain analogies with serum precipitation.

As stated, bacterioprecipitins are quite specific. In the case of colon bacilli, immunization with one strain results in precipitins for related strains, but to a much less extent than for the homologous strain. Norris found that sera of rabbits immunized to four species of the colon-typhoid group precipitated filtrates of all the species of the colon-typhoid group tested, but more quickly and more copiously in case of the homologous filtrates, and in high dilutions only in the latter. It is assumed that the filtrates contain diverse precipitinogens which on immunization give rise to numerous partial precipitins. Recently, Vincent has made use in the diagnosis of meningitis of the fact that a precipitate develops when antimeningitic serum is added to the cerebrospinal fluid, made clear by centrifugation, from cases of epidemic meningitis.[2]

[1] *Blood Immunity and Blood Relationship*, Cambridge, 1903.

[2] Ascoli's precipitin-test for anthrax, which is regarded as of great value to veterinary diagnosis, is made by adding anti-anthrax serum to extracts of infected organs, the precipitable substance in which is resistant to boiling and decomposition. See Hecht: "Die Präzipitindiagnose des Rauschbrands mit einem Beiträg zur Frage der Thermoresistenz des Präzipitinogene," *Centralbl. f. Bakt.*, I. O., 1912, lxvii, 371.

Agglutinins and Agglutination.—Gruber and Durham, while studying Pfeiffer's phenomenon, were the first to observe that agglutination is a specific reaction. The reaction of agglutination was applied almost at once as an aid to the diagnosis of typhoid fever by Grünbaum and by Widal. Its use has extended to other infectious diseases as well as to the tentative identification of bacteria suspected of causing infectious processes. Other objects besides bacteria are subject to agglutination, *e. g.*, red blood corpuscles may be agglutinated not only by normal and immune[1] alien sera, but also by toxic substances of animal, plant, and bacterial origin. Certain bacteria also produce hemagglutinins, and it is believed that certain thrombi observed in infectious diseases owe their origin to agglutinins derived from bacteria. The serum of various species contains agglutinins for the corpuscles of other individuals of the same species (iso-agglutinins), but auto-agglutinins do not seem to occur. In human beings Landsteiner and others have shown that the occurrence of iso-agglutinins and the agglutinability of the corpuscles afford the basis for a grouping of individuals which should be taken account of in transfusion because of certain possibilities of danger, especially when the donor's serum agglutinates the patient's corpuscles.

Normal serum in general contains small quantities of bacterio-agglutinins also, especially for the bacteria of typhoid fever, cholera, and dysentery, as well as for colon and pyocyaneus bacilli. When a normal human serum has a relatively high agglutinative power against a given bacterium the possibility of a previous infection must be considered. Immune as distinguished from normal agglutinins develop either in spontaneous infections or as the result of artificial immunization by various procedures. The power to cause agglutinins to form in the animal body is possessed by bacteria in general, but some have this power in higher degree than others. The agglutinability also varies; the typhoid bacillus when first isolated, for instance, is sometimes quite inagglutinable.

Agglutinins, theoretically, are free receptors with two atomic groups, one haptophore, whereby they unite with the antigen, and one that causes the alteration in the bacterial cell on which agglutination depends. By heating for some time between 60° and 80° C., by exposure to acids and alkalies, and by long standing, this second group may be lost and the agglutinin is transformed into agglutinoid, which may prevent agglutination by the agglutinin, because the latter finds no place to attach itself to the cell. Agglutinins withstand digestion with pepsin, but not prolonged tryptic digestion. When serum is dried and carefully preserved agglutinins remain intact for months and years. The power in different animals to form agglutinins varies.

At one time agglutinins and lysins were thought to be the same substances; but it has been found (1) that the serum of cholera and typhoid convalescents may be strongly bactericidal, while the agglutinating power is no more marked than in normal serum; (2) that in certain

[1] By immune in this case is meant the serum of an animal injected or immunized with the corpuscles of another species.

cases immunized animals give only agglutinins and not lysins; (3) that immune serums may lose their lytic power but retain their agglutinating property, and *vice versa;* (4) that in immunization the curves of agglutinating and bacteriolytic substances as they appear in the blood are not always parallel.

As agglutination takes place the corresponding agglutinin is removed from the serum. It is consequently possible by means of selective absorption to demonstrate the presence of more than one agglutinin in the same serum.

Immune serum may agglutinate organisms that are closely related to the bacterium acting as antigen. The typhoid-colon group furnish many examples of this "group agglutination," which is dependent on the presence of various agglutinins. Generally the agglutinin for the organism acting as the antigen is present in the largest quantity, and it is therefore spoken of as the chief agglutinin; while the weaker agglutinins for the organisms are called partial or adventitious or common agglutinins. Park and Collins have shown, however, that if immunization is continued for a long time the relative amounts of specific and non-specific or common agglutinins may vary from time to time, and that the common agglutinins may equal or exceed the chief in amount. Durham offers the following explanation of group agglutination: "The typhoid bacillus contains certain constituents, agglutinogenic molecules, which one may designate as *a, b, c, d,* and *e;* these differ among themselves in unknown respects, but each is able to stimulate the formation of a corresponding agglutinin. The serum, then, would have the agglutinin molecules *A, B, C, D,* and *E,* also differing among themselves, but having at least one property in common—that of causing agglutination of the typhoid bacillus by uniting with their corresponding agglutinogenic molecules. In this sense nothing could be more specific. *Bacillus enteritidis,* closely related to the typhoid organism, may possess the agglutinogenic molecules *c, d, e, f, g,* and *h,* and following the principle expressed above would stimulate, in the body, to the formation of agglutinin molecules *C, D, E, F, G,* and *H.* Inasmuch as the agglutinogens *c, d, e* are common to the two bacilli, the agglutinins *C, D,* and *E* would affect either of the two organisms. The typhoid serum would contain five agglutinins for the typhoid serum and only three for *Bacillus enteritidis,* consequently the action would be stronger against the typhoid bacillus." It is a general rule that agglutinins, specific as well as common, set free by one bacterial species, may be removed from the serum by adding sufficient quantities of that species. Other bacteria would remove those common agglutinins for which they have the proper affinity.

At first, agglutination was regarded as the result of an abnormal viscidity of the bacteria or as due to the formation of a sticky precipitate upon them, but lately Bordet's conception of agglutination is similar in nature to the precipitation of colloid suspensions and has received strong support.[1] Agglutination occurs after agglutinin has combined with the

[1] Landsteiner and v. Esler: *Central. f. Bakt.,* 1 Abt., Orig., 1905, xxxix, 309.

bacteria[1] (forming the so-called agglutinin-bacteria), which become clumped and settle down, provided salt is present (Joos). Like certain other particles, bacteria behave like negatively charged particles in electrical currents in that they migrate to the positive pole. The cation of the salt, being positively charged, attracts bacteria or other particles and neutralizes their electrical charges with the formation of clumps that fall out of suspension (Billitzer). Now the role of agglutinin appears to be to reduce the amount of negative electricity the bacteria carry and thus to render them more susceptible to the clumping action of the salts present in the fluids. All salts clump agglutinin-bacteria more readily than they do normal bacteria. The mechanism of specific precipitation is regarded as identical, only the particles are smaller. Agglutination and precipitation depend, then, according to this view, on the action of salts on the electrical charges that keep the particles suspended.

Allergy.—From what has been said we would expect that the protective reactions induced by an antigen would be reënforced on the reintroduction of the antigen, but it might seem, at any rate at first glance, as if under certain circumstances this is not the case, because peculiar, often violent, and even fatal symptoms may set in when the antigen is introduced again. This phase of immunization has been studied actively and has been designated as anaphylaxis (Richet), which means the reverse of prophylaxis, as hypersusceptibility, as protein sensitization (Vaughan), and as allergy (v. Pirquet), which means changed reactivity.

The Experimental Basis.—It is not feasible to go into the details of the vast amount of work on which rests our understanding of allergy. As a rule, an animal once subjected to the influence of a foreign protein, vegetable, animal, or microbic, which must be introduced as such into its blood or tissues, develops a condition which manifests itself by special symptoms when the protein is reintroduced. It takes some time, at the very least a few days, for this condition to develop; gradually a maximum intensity is reached, after which there is a slow return to the normal, a curve being traced that is like the antisubstance curve. Allergy may be established with respect to many protein substances, notably serum, bacteria, and their derivatives, milk, egg-white, red corpuscles, and various more or less pure proteins.[2] These are substances with antigenic powers and the allergic reactions follow the same laws as to specificity as antigen reactions in general. A passive allergy, analogous to passive immunization, is obtainable by the injection of a normal animal, particularly the guinea-pig, with the serum of animals or persons already allergic or sensitized (Gay and Southard, Otto), and this transferred condition is specific in the same way as the allergy of the donor. This fact, which shows that allergy depends on specific substances in the blood, is the basis of the conception of allergy which now prevails,

[1] The various conceptions concerning this union are discussed by Craw: *Journal of Hygiene*, 1905, v, 113.

[2] Wells and Osborne: *Jour. Infect. Dis.*, 1911, viii, 66.

namely, that on the introduction of the antigen new substances of the general structure of amboceptors are developed, which unite the complement with the antigen, the complement by virtue of its digestive powers setting free substances that in proper concentration cause the symptoms of allergy. In other words, the action is regarded as a specific proteolysis in the blood and tissues, the toxic substances thus produced being split-products or possibly preformed poisons (endotoxins) set free. Substances causing the general symptoms of allergic intoxication in guinea-pigs are obtainable *in vitro* by splitting up bacteria and egg-white with chemicals (Vaughan); by the action of immune serum and complement on the corresponding antigen (Friedemann, Friedberger); by the action of complement on the precipitate produced in serum by specific precipitin (Friedberger); and by letting bacteria like the pneumococcus, the gonococcus, and the like, digest themselves (Rosenow). At present, then, our explanation of allergy centres on the view that parenteral protein digestion plays the essential part, the digestion being accomplished by an amboceptor-complement mechanism.

The symptoms of the allergic reaction vary a great deal, depending on the species and the quantity of toxic substances. In the guinea-pig the reinjection of antigen may give rise to explosive symptoms, death resulting in a few moments from asphyxia due to spasm of the bronchi; when death does not occur immediately there is a marked fall of the temperature, and when the reaction is very mild there may be fever. In dogs there is a marked fall of blood pressure due to splanchnic action, and in rabbits occur respiratory disturbances, prostration, and a cardiac rigor; sometimes local changes of œdema and necrosis develop. Common in all these conditions is temporary loss of complement, loss of coagulability of the blood, and leukopenia.

When the animal recovers it is insensitive for two or three weeks to further injections of the antigen (anti-anaphylaxis or anergy). There is some question whether this state is produced only by the protein used for sensitization. It was first thought that it concerns an antitoxic immunity, but there is no incubation period, and the serum of refractory animals does not protect. It seems most likely that the refractory state results because the antibody or ferment is bound by the foreign protein; in other words, that it concerns what is termed the negative phase in antibody formation.[1] It has been urged against this conclusion that, according to some observers, the serum from refractory animals actually confers sensitiveness when injected in fresh animals.

Allergic Phenomena in Man.—A variety of allergic phenomena occur in man. In the first place the injection of therapeutic serum in highly exceptional instances may cause dyspnœic symptoms not unlike those in the acute reaction in guinea-pigs; just how sensitization has occurred in such instances is a matter of speculation. More familiar is the reaction called "serum disease," which sometimes appears from eight to twelve days after the injection, in this case part of the serum seems to remain

[1] Weil and Coca: "An Experimental Study of Anti-anaphylaxis," *Proc. Soc. f. Exp. Biol. and Med.*, 1912, ix, 82.

unchanged until enough antibody has developed to cause a sharp reaction. If serum is reinjected after some time, thus reproducing the experimental conditions, the reaction may develop almost immediately or after three or four days. The symptoms are familiar: Urticaria, œdema, articular pain, swelling of the lymph nodes, leukopenia, fever, weakness, and sometimes collapse.

In the second place, human diseases present a rich field for the study of allergic phenomena, to some of which attention may be directed. In infectious diseases, especially those which do not, like diphtheria and tetanus, depend on the secretion and absorption of typical toxins, there is much to indicate that many of the symptoms result from the interaction of the antibodies or ferments of the host and the microbes, that the symptoms are, so to speak, allergic manifestations due to toxic substances arising or set free in the course of the destruction of the microbes. In the light of this view the incubation period would represent the time necessary for the formation of sufficient antibodies to break up the microbic proteins. In many infections this period corresponds closely in length to the period preceding the acme of antibody formation under experimental conditions. This is illustrated well in smallpox and vaccinia, and as here the cutaneous lesions contain the virus it is reasonable to regard these lesions as the result of the reactions between the antibodies and the virus. On daily vaccinations of a susceptible person, v. Pirquet found that the maximum reaction occurs at the same time about all points of inoculation, namely, when it occurs at the first point; here, then, the antibodies educed by the first vaccination on reaching the required concentration, act in the same way and with the same result on the virus deposited in the skin from day to day. In serum disease the incubation may be shortened greatly in persons previously injected with serum, and so also on revaccination of previously vaccinated persons, accelerated reactions occur; and varioloid is regarded as an atypical form of smallpox in a partially immune person. Undoubtedly the incubation and clinical course of other infections is influenced by heightened reactivity on the part of the body caused by previous attacks.

Jenner[1] probably was the first to recognize what we now speak of as allergic reactions to infectious material. He observed that the skin of persons having had smallpox or cowpox reacted peculiarly to the application of variolous matter. Thus in a woman who had cowpox thirty-one years before she was inoculated with variolous matter, "an efflorescence of palish, red color soon appeared about the parts where the matter was inserted, and spread itself rather extensively, but died away in a few days without producing any variolous symptoms." That common wound infection is excluded seems clear because he observed the phenomenon so regularly under these special conditions that he was led to comment as follows: "It is remarkable that variolous matter, when the system is disposed to reject it, should excite inflammation on the part to which it is applied more speedily than when it produces the

[1] *Inquiry into Causes and Effects of Variola Vaccinæ*, etc., 1789, p. 13.

smallpox. Indeed it becomes almost a criterion by which we can determine whether the infection will be received or not. It seems as if a change, which endures through life, had been produced in the action, or disposition to action, in the vessels of the skin; and it is remarkable, too, that whether this change has been effected by the smallpox or the cowpox, that the disposition to sudden cuticular inflammation is the same on the application of variolous matter." In this remarkably clear statement we note with special interest the intimation of the diagnostic value of the reaction.

The allergic state of the infected body is shown then by reactions which take place when the substance causing the infection is introduced. The tuberculin and other tests like it are based on this circumstance. Reaction to tuberculin is developed best in the tuberculous person or animal, but it is obtainable also after active sensitization by means of tubercle proteins, and passive transfer of the reaction to guinea-pigs has been accomplished in a variety of ways. Since the introduction of vaccine therapy, fever and malaise, acute changes in local lesions, and sometimes reactions at the site of the injection of the vaccine have been observed in many subacute and chronic infections; diminution of complement and a fall in opsonin—"negative phase"—generally accompany this reaction. Noguchi has shown that in syphilitics, extracts of the *Treponema pallidum* which he has grown in pure culture give a characteristic cutaneous reaction. When inoculation of gonococci was begun it was soon observed that acute reactions may develop in the lesions. Irons (1908) described in detail the reaction as it appears after the injection of gonococci in arthritis. This reaction, which is analogous to the general tuberculin reaction, is characterized by "a rise in temperature, often only slight, an increase in pain and tenderness in the affected joints, and occasionally some increase in swelling, and a variable degree of malaise. The symptoms follow the injection in from eight to twelve hours and commonly last twenty-four hours. Frequently there is a decided tenderness at the site of the injection, greater than after the inoculation of the same dose of the same proportion in normal subjects. Commonly there is marked redness and œdema lasting from twenty-four to forty-eight hours." Usually there is a slight leukocytosis during the first twenty-four hours. A similar reaction with increased pain and swelling of the lesions occurs in other forms of gonococcal localization. Quite recently, Irons has demonstrated that in gonococcal infections a cutaneous reaction is easily obtainable by applying extracts of gonococci to the skin in the same way as tuberculin is applied in v. Pirquet's test.[1]

[1] The serum of animals immunized against gonococci has been found to harbor various specific antibodies—agglutinins, precipitins, bactericidal and opsonic elements, and bodies that in connection with gonococci bind complement—and from the study of the action of such serum, on various strains of gonococci, it appears that the gonococcus group is made up of races with distinct affinities, so that the extracts or mixtures of gonococci used for diagnostic purposes had better be derived from several distinct strains. It is interesting to note also that there is a chemical relationship between the gonococcus and the meningococcus because it does not seem possible to differentiate absolutely one from the other by means of the complement fixation test; this also seems to hold true with respect to the cutaneous reaction.

It is self-evident that as the details of these newer allergic reactions are worked out, useful adjuvants will be added to our means of diagnosis of occult infections.

That many "idiosyncrasies" with respect to foods—strawberries, cheese, fish, oysters, buckwheat, pork, eggs, cows' milk, etc.—are expressions of allergy can hardly be doubted. Striking examples of sensitiveness to milk and egg-white ("egg asthma") have been described. Not many cases of alimentary allergy, or anaphylaxis, have been studied thoroughly from this newer point of view as to their nature, but in one case of intolerance of pork it was found that the serum of the patient introduced in guinea-pigs produced allergy to pork (passive anaphylaxis).

It has been suggested that under certain conditions the proteins of the body itself may become so changed—"heterologized"—as to acquire antigenic powers, and on reacting with the antibodies give rise to toxic substances. It would be particularly at the seat of severe lesions, such as are produced in certain forms of chronic tuberculosis, and in burns, for instance, that this change most likely would occur. Claiming support from experiments, some would account in this way for the fall of temperature, convulsions, and delirium that sometimes develop unexpectedly several days after a burn. Drug eruptions, *e. g.*, those from iodide and bromide, may rest on a similar basis. As placenta, amniotic fluid, and fetal serum may act as foreign proteins in adults of the same species, the idea that puerperal eclampsia, "the disease of theories," is an anaphylactic condition has been advanced.

The skin, as noticed, presents many interesting phenomena from the allergic point of view; the lesions of serum disease, the eruptions of infectious diseases, the urticarias, and other manifestations of the absorption of foreign proteins from the digestive tract (alimentary anaphylaxis), the allergic reactions of infectious diseases, all indicate that the skin not only has a marked affinity for foreign proteins, but that it also is a sensitive reagent for the various products of parenteral proteolysis. To what extent other tissues have similar relations is not clear, but hay fever and certain forms of asthma appear to be allergic phenomena, and certain hemorrhagic lesions of the intestines (enteritis anaphylactica) may also be of this nature.

Allergy and Immunity.—In regard to the apparent incompatibility between immunity and the allergic state, we observe that in the so-called sensitized body the specific foreign protein may be split up rapidly by the complement, acting through the specific amboceptor, so that toxic substances are set loose in toxic quantities; in the normal body symptoms do not develop probably because the process proceeds slowly and gradually. Now, infectious microbes are destroyed by the same mechanism of proteolysis, and when small quantities are introduced, as often must be the case in natural infections, the microbes may be disposed of in this way before they multiply sufficiently to supply toxic doses of poison, and the process of destruction will occur with greater promptness in the sensitized, that is more or less immunized, body "when the system is disposed to reject" the foreign protein. This is immunity, natural and acquired, based largely on prompt, early reaction.

In reality the allergic state is not one of greater susceptibility, but one of greater reactive, and consequently in infectious diseases, of greater protective power, the actual susceptibility to the same poisons being probably the same in the average allergic and normal body. Hence there is no incompatibility between immunity and allergy, the allergic symptoms being manifestations of antibody-antigen, *i. e.*, proteolytic reactions in the blood and tissues of the living body.

PART I

BACTERIAL DISEASES

CHAPTER II

TYPHOID FEVER

By THOMAS McCRAE, M.D.

Introduction.—Typhoid fever is a general infection with the *Bacillus typhosus* characterized especially by involvement of the lymphoid tissues, usually by hyperplasia and ulceration of Peyer's patches, enlargement of the spleen, and parenchymatous changes in certain other organs. There is no uniformity in the name given to it in various languages. While there may be objections to the name "typhoid," yet this is so firmly established that usage has sanctioned it and there is no confusion from it. We designate the causal organism as the *Bacillus typhosus*. In Great Britain the term "enteric fever"is in common use.

There is no disease with a more interesting history. Long confused with typhus fever, the distinction brought about slowly, it stands as an example of the difficulties which may attend the recognition of a disease. The views as to its nature have gradually changed. For a time regarded especially as a disease of the intestines, later we learned that it was primarily a general infection, with secondary intestinal lesions. Then it was found that in some instances there was an absence of intestinal lesions, and that other organisms than the *Bacillus typhosus*, although closely related, caused similar lesions. Local infections were proved to be possible without a general infection. In some instances the disease occurred as a terminal infection without any intestinal lesions.

In the explanation of the symptoms we have gone through different stages. Before the causal organism was discovered, the features of the disease were supposed to be principally due to changes occurring in the body of the patient. After the discovery of the causal bacillus, the specific infection and its results were held to be the most important, but, as Ewing pointed out, we may have given too little attention of late to the body itself. While the action of the bacillus and its products are important, yet much may be due to changes in the tissue cells of the body. After these have been injured or killed by the specific organism they will give rise to certain derivatives which are injurious in themselves and also appear to have an accumulative action. An analogy is suggested in some forms of acute yellow atrophy of the liver and also

possibly in some of the cases of severe toxemia in pregnancy. There are also suggestive findings in regard to the metabolism in typhoid fever. In many instances there are two marked changes: (*a*) A great increase in the urea nitrogen of the urine and (*b*) an increase in the ammonia and amido-acid nitrogen. It has been found that in some cases these are comparable to conditions in diabetes, leukemia and grave jaundice. The lesions found in the liver also support this view, especially as in some instances alterations like those found in acute yellow atrophy have been described. These suggest that changes in the body cells may be responsible for many of the symptoms and this may apply especially to the patients who die late in the disease with severe toxemia.

As regards the bacillus, its toxins, the question of immunity, the explanation of relapse and other problems, there is much to learn. The length of time during which bacilli may live in the body after recovery from the disease shows that this does not necessarily mean the destruction of all the bacilli in the body.

The stamping-out of typhoid fever is one of the great tasks before the profession of this country. A disease more of rural communities than of cities, its control offers many difficulties. The story is such an old one that little attention is paid to it. We of the profession shrug our shoulders and wonder at the apathy of the civic authorities. Are we guiltless? Every patient with typhoid fever means infection from a previous one. Disinfection is often left in the hands of people who do not realize the importance of its being thorough, and it is no easy task for the physician to see that it is carried out. Too often he does not realize his own responsibility and is thoroughly satisfied if he brings the patient well through the attack, heedless of the danger to the community.

We are utterly illogical in our attitude to typhoid fever. We consider an ounce of cure worth many pounds of prevention. Nature is "careful of the type, careless of the single life," but we reverse her methods. A community is exposed to infection year after year and little is done for the many, but for the individual with the disease, hospitals, physicians, and nurses work day and night. Think of the labor expended on one hundred patients to save the ten who are kept from death by care. How much better to remove the necessity of it.

From the mere side of the cost to the community, typhoid fever is important. Estimates may vary as to the value of the 35,000 people who die in the United States every year from typhoid fever. To be added to this is the cost of the illness of the 350,000 patients who recovered. To do this with accuracy is difficult, but it is evident that the money cost of the disease is enormous.

While typhoid fever with its great variety of symptoms has perhaps the first place in clinical interest for us, yet it is to its prevention that we must devote the greatest attention. Perhaps nothing would aid this so much as improvement in the administration of the health boards through the country. It should be possible whenever an outbreak of typhoid fever occurs to immediately have an efficient sanitary authority with proper equipment take charge of the situation. If a State would establish such a bureau, get a good man at the head of it, and give him

sufficient powers, the occurrence of typhoid fever in that State would rapidly diminish.

Etiology.—The typhoid bacillus is the essential cause of the disease, but the means by which it gains admittance to the body are very various. These "intermediary bodies," however, are only carriers, for the bacillus is dependent on man for its existence, and although it may live for a time in water or on various articles, yet its life in such situations is comparatively short. Man is the cause of the continuance of the disease, but there are many factors which influence the conveyance of bacilli from one individual to another. In this connection the value of protective inoculation has been thoroughly established, and in all statements regarding the dangers of infection, the influence of the protection given by this must be remembered.

Geographical.—Typhoid fever is one of the most widespread of the infectious diseases. It occurs in the tropics and in far northern and southern latitudes, at sea-level and in the mountains, in the city and in the country, and practically wherever man may go and local conditions do not prevent the dissemination of the disease. The *B. typhosus* has about the same limits of latitude and longitude as man himself, and no country or race is known to be immune from the disease. The character of the water-supply and the means of disposal of excreta must be regarded as the most important factors which influence the occurrence of the disease in communities. When men are living together under unusual conditions, such as an army in the field, other factors appear and have an important influence. But under any conditions or climate the essential thing which governs the occurrence of the disease *is the method in which the excreta are disposed.* Given the occurrence of typhoid fever other factors become active, but, as a rule, the statement stands that "the history of this disease justifies us in stating that wherever and whenever men congregate and live together without adequate provision for disposing of their excrement, there and then typhoid fever will appear." The report of the Commission for the Study of Typhoid Fever in the Spanish-American War (Reed, Vaughan, and Shakespeare) is especially valuable, and is one of the best contributions to our knowledge of the disease.

There may be marked differences in the character of the disease in a community from one year to another. It has long been noted that a newcomer, if he contracts the disease, is likely to have a more severe attack than the average of the residents. The patients at the beginning of an epidemic may show marked differences in the severity of the attacks from those seen subsequently.

Typhoid fever differs in its method of spreading from the acute infectious diseases. It does not extend over a continent as influenza, nor does it strike the majority of those exposed to it as smallpox or measles in an unprotected community. The disease may be contracted in Europe and carried to the United States during the attack itself, or if we consider the length of time during which typhoid bacilli may remain in the urine, it is no exaggeration to say that a man may scatter infection around the world.

War.—As has been said, an army has two foes—"bacilli and men," and of these the former is by far the more dangerous. It is not possible to recognize with any certainty the nature of epidemics which visited armies earlier than the latter half of the nineteenth century, but some of the accounts suggest typhoid fever. In the wars of the last fifty years typhoid fever has played an important role. In the American Civil War there were in the northern army 75,361 cases among the white troops with 27,056 deaths, and 4094 cases among the colored troops with 2280 deaths, while the large percentage of deaths suggests that there were probably many more cases of the disease than were recognized. In the Franco-Prussian War of 1870–71, among the German troops there were 73,396 cases of typhoid fever with 8789 deaths, which comprised 60 per cent. of the total mortality. The incidence in proportion to strength in the German army was very high. There was typhoid fever in every corps of the army at the beginning of the war and two factors influenced the prevalence of the disease—the troops carried infection with them and were campaigning in a country in which typhoid fever was common. In the Spanish-American War the highest incidence of typhoid fever was among the troops who never left the United States. Among 107,973 men there were 20,738 who had typhoid fever with 1580 deaths. It was found that 90 per cent. of the volunteer regiments had men with typhoid fever within eight weeks after going into camp and that epidemics were as marked in the North as in the South.

The importance of the "auto-infection"—if the term may be used—of an army with typhoid fever is well brought out by the results of many campaigns. Thus in the Afghan War of 1878–80, the British troops brought the disease with them from infected areas in India, and it was carried to localities where previously it was unknown. In the Egyptian War of 1882, certain regiments carried the disease with them, while other regiments, which entered the same campaign free from typhoid fever, escaped, despite the fact that they drank bad water. In the Chitral campaign of 1895, typhoid fever was carried in by the troops. There was a marked difference in the occurrence of the disease among the privates and officers, the latter escaping almost entirely. The men were much more crowded together, the close contact favoring infection.

It is evident that the problem of etiology differs somewhat in civil and military life. There are several factors in this: (*a*) The greater difficulty in disposal of the excreta which leads to infection in various ways, as the water-supply may be contaminated, the bacilli blown about with dust or carried by flies. (*b*) The close contact of men crowded together favors direct infection, while clothing, blankets, and tents may become soiled and contaminated. The influence of camp life on troops who had a good water-supply was well shown at Jacksonville, Florida, in the fall of 1898. There were about 30,000 people in the city with very few cases of typhoid fever, while among the troops near by, with the same water-supply, the disease was very prevalent.

Season.—As a rule the disease shows a fairly uniform relation to the time of the year, in Europe and America being most prevalent in the

autumn months. Of the 1500 cases of this series,[1] 840 (56 per cent.) were admitted in the months of August, September, and October. The disease usually persists on into the winter months, with a decrease after December, the smallest number of cases occurring during the spring months. But in the majority of American cities there is a certain prevalence throughout the year, no month being without a few cases. Epidemics may occur at any season if there be infection of the water-supply.

We have not any satisfactory explanation for this seasonal variation. It is so general and occurs apart from local conditions with such regularity, that some condition associated with the development of the typhoid bacillus must be concerned. The disease is likely to be especially prevalent in hot and dry seasons, but the contrary is not necessarily true. It may be that the state of the ground water has some influence, as when this is low the sources of the water-supply are more likely to drain a wider area and thus the chances of infection are greater. This applies especially to rural districts. There is also a great increase in the number of persons exposed to infection during the summer months. People from the cities spend their vacations in the country where there is usually much more chance of infection.

Sex.—There does not seem any reason why one sex should be more subject to the disease, unless the more active life of men gives greater chances of infection, but hospital statistics show a larger proportion of males. In this series, 1062 were males and 438 females (2.4 to 1), the ratio in the whole clinic being about 5 males to 4 females. It is easy to understand why females should always be fewer in hospital statistics, yet even in childhood there is usually a preponderance of males.

Age.—The disease is one especially of youth and early adult life and in this series the incidence was:

	Number	Per cent.
Under one year	2	0.013
1 to 15 years	231	15.0
15 to 20 years	253	17.0
20 to 30 years	680	45.0
30 to 40 years	227	15.0
40 to 50 years	88	6.0
50 to 60 years	8	0.5
60 to 70 years	11	0.7

Among 19,586 cases in the London Fever Hospitals from 1871 to 1904 the distribution was: Under 5 years, 3.4 per cent.; 5 to 10, 13 per cent.; 10 to 20, 41 per cent.; 20 to 30, 26 per cent.; 30 to 40, 11.6 per cent.; 40 to 50, 4 per cent.; 50 to 60, 0.8 per cent.; and over 60, 0.2 per cent. During the first year of life the disease is rare, and there is then a gradual increase up to about the fifteenth year, from which age up to forty the disease is most prevalent. After forty the number gradually diminishes, but it is by no means infrequent even in old age.

Constitution and Mode of Life.—As regards the bodily condition there does not seem any proof of the correctness of the popular idea that an attack of typhoid fever means a previously "run-down" condition; on

[1] This article is based on the experience of the Johns Hopkins Hospital series of 1500 cases and 105 autopsies.

the contrary it is often those in the best physical state who contract the disease. The social surroundings do not seem to play much part. The water-supply of the community is usually much the same for rich and poor. Given, however, a case in a household and the chances of infection of other members are greater among the poorer classes, where crowding is more common and isolation and disinfection are likely to be less efficient. As regards occupation, there does not seem to be any special peculiarity, except in active military service. Physicians and nurses who are handling patients are in some danger of infection.

Gastro-intestinal Conditions.—That gastric conditions may have some influence may be thought probable, but is not proved. On general grounds a normal gastric juice should afford more protection than one deficient in acid and ferments, but the typhoid bacillus is probably not destroyed by ordinary gastric juice. As regards gastro-intestinal disturbances, the studies of the Spanish-American War Commission show that these do not predispose to typhoid fever. Thus, of 9481 men who had previous diarrhœal attacks only 648, or 6.8 per cent., had typhoid fever, while of 46,348 men who had no preceding diarrhœa, 7.097, or 15.3 per cent., had the disease, and more than 90 per cent. of the typhoid fever patients had no preceding intestinal disorder.

Certain conditions are thought to confer relative immunity, among which are pregnancy and the puerperal state. Women who are pregnant may be less exposed to infection. In the present series, among 438 female patients there were 6 who were pregnant. Taking the figures of Curschmann, Goldammer, and Martinet with this series, among 3355 females patients there were 93 who were pregnant (2.8 per cent.). In the puerperal state and during lactation the disease is rare and there were only 2 instances in this series. Other diseases, such as tuberculosis and the acute exanthemata, are thought to give immunity, but this seems doubtful when the number of instances of the coexistence of typhoid fever and these diseases is considered.

Modes of Infection.—These are numerous, and while in a sudden epidemic it may be possible to determine the source of infection with certainty, in the steady endemic occurrence it may be very difficult. Take any ordinary community with its usual number of cases every year, and in many of these the source of infection cannot be determined positively. One thing we are sure of—the bacilli came from another patient, the moral of which is obvious.

1. Direct Infection.—This is probably much more frequent than has been supposed. Wherever a large number of persons are crowded together it is a prominent factor. It also occurs to a considerable extent in houses, especially where there are crowded conditions. Those associated with or waiting on the patient may be careless and carry the bacilli on their own hands to the mouth, or infect the food. Probably those nursing a patient always get some bacilli on the hands and without great care others may be infected. The more carefully epidemics are studied the more often will cases of contact infection be found. Among the last 500 patients of this series, there were 55 who came from houses in which were other patients with the disease, and in many instances

they had been nursing the patients before becoming sick themselves. During the same time there were 7 trained nurses who had been nursing patients with typhoid fever outside the hospital and 5 who were nursing in the wards. There was 1 worker in a laboratory who was handling typhoid bacilli and 1 orderly waiting on patients with the disease. This gives a total of 69 out of 500 who were exposed to more or less direct infection. That contact infection does not always play much part is shown by the report of Smith on the conditions in Belfast, where from 1898 to 1903 there were 12,900 cases of typhoid fever in 11,017 houses: that is, in 85 per cent. there was only one case to a house.

Even in hospitals there is some danger, despite all precautions. Schuder has estimated that 3.3 per cent. of all cases are due to hospital infection. It is stated that from 1881 to 1889 of the cases in the German army, 6.3 per cent. were from hospital infection. Dubus collected 145 instances among 5989 cases (2.4 per cent.). In the Johns Hopkins Hospital there have been 31 instances of infection occurring in persons in the hospital. Of these 5 were physicians, 3 of whom were in the medical wards, the others being on the surgical staff. There were 15 nurses, of whom 11 had been nursing patients with the disease. Of the 8 patients, 3 were in surgical wards and not in contact with patients who had the disease. Four cases among patients occurred in a ward epidemic. There were 2 orderlies, both of whom were working with typhoid patients, and it is difficult to understand why so few of them have been attacked, as they are often careless.

There is great danger of direct contagion in children's hospitals, especially if the beds are very close together or the convalescents are allowed to play with other children. Dubus[1] mentions one hospital in which there were 27 instances of direct contagion in three years. If the children are bathed in the same tub or the same cloths used the danger is increased.

2. Water.—This must be regarded as an important means of conveyance and in large epidemics, where the extent is influenced by the amount and freshness of the infection, it usually plays a large part, as well as in the yearly incidence in many communities. Schuder, in the study of 638 epidemics which occurred from 1870 to 1899, found that the infection was carried by water in 71 per cent. Typhoid bacilli have been found in water in a considerable number of cases. In the sudden outbreaks it may be very easy to trace the source of infection to the water-supply, for such epidemics are often "explosive," but in places where there is only the usual number of cases this may be difficult.

The steady decrease in the disease in communities as the water-supply is improved is perhaps one of the best proofs of the importance of water-borne infection. In Hamburg from 1885 to 1888 there were 15,804 cases of typhoid fever. The water-supply was taken from the Elbe, not far from the point where the sewers discharged. The neighboring city of Wandsbeck, with a separate water-supply, was almost free from the disease, giving a demonstration as striking as that of Altona in the

[1] *Thesis*, Paris, 1905.

cholera epidemic of 1892. In Paris, with a better water-supply, the death rate from 1882 to 1902 was reduced from 142 to 17 per 100,000.

Ice has rarely been proved to be the means of conveyance of typhoid bacilli, although frequently under suspicion. The report of an epidemic due to ice at the St. Lawrence State Hospital, near Ogdensburg, N. Y., is given by Hutchings and Wheeler. The institution had been free from typhoid fever for some time when, early in 1903, they had an epidemic of 39 cases. Six days before the appearance of the first case, ice from a new ice-house had been used. This had been filled in February by ice taken from the St. Lawrence River three miles below Ogdensburg, in which city there had been typhoid fever. The sewage from Ogdensburg was emptied into the river above the point from which the ice was gathered. In the ice there were masses of foreign matter and sediment and typhoid bacilli were grown in cultures from these.

3. Food.—(*a*) *Milk.*—There have been many epidemics in which all the evidence pointed to milk as the source of infection. Schuder, among 638 epidemics, found infected milk to be the cause in 17 per cent. In many of these it is not possible to obtain direct bacteriological evidence, but the facts are so suggestive as to be almost conclusive. When the disease is confined to the users of milk from one farm and there is strong probability of infection from a patient, there is little doubt of the proof. In other cases the infection may occur during the transfer of the milk in the city, either in the establishments which handle it or in small distributing stores. Ice-cream may be a source of infection and may be very difficult to trace.

An epidemic in Palo Alto, California, in 1903, was traced to infection through milk (Fish, Mosher, and Snow). Among 900 people who obtained milk from the same supply, 232 had typhoid fever; of these, 216 were apparently due to infection from the milk, while 16 may have been due to secondary infection, although all but two used the infected milk. That is, 98 per cent. of the typhoid fever patients had used the one milk supply and 26 per cent. of the users of this supply had typhoid fever. The water used for washing the cans and also at times for diluting the milk was obtained from a creek which was infected by the drainage from houses in which there were patients with typhoid fever.

It may be difficult to trace the exact source of infection but there are probably more instances than are generally supposed of infection of milk in small stores and milk depots. Should there be a patient with typhoid fever in the same building it can easily be seen how the milk may become infected by the same person waiting on the patient and handling the milk. The amount of milk taken probably influences the chance of infection. Thus in the Palo Alto epidemic a larger percentage of patients was found among those who had two deliveries of milk a day, and presumably used more, than among those who had one.

Butter and Cheese.—It is doubtful if these are frequently a source of infection. Typhoid bacilli may live for a varying period in butter, some observers giving as long as twenty-seven days, but in these experiments the butter receives a heavy inoculation under conditions favorable for the organisms. Under ordinary conditions their duration of life is not likely

to be long, owing to the number of vigorous saprophytes, the chances of being washed out with the buttermilk (as happens to nine-tenths of the bacteria in the cream), and the salting. The danger of infection from cheese must be practically *nil*, owing to the long period of ripening.

(*b*) *Shell-fish.*—There are a considerable number of instances of infection by these. In this country oysters and clams are most frequently under suspicion, and in England, mussels and cockles have also to be considered. It may be easy to prove that they have carried infection if there be an epidemic, but it is likely to be very difficult in sporadic cases. Shell-fish may be sent to considerable distances and widely distributed; hence the cases are not so likely to be associated as in a milk epidemic. One of the first epidemics traced to infection by oysters was that in Middletown, which was studied by Conn. This occurred among students, and at first it was difficult to find any common source of infection. Investigation showed that this could only have been from oysters which had been eaten at several dinners on the same evening. The oysters had been put into a small creek, for the purpose of "fattening," within one hundred yards of the outlets of a number of sewers, one of which came from a house in which there were two patients with typhoid fever. In England there have been many instances.

In all shell-fish, the danger comes from the water in which they are put, either for "fattening" or until they are wanted for use, as for convenience they are likely to be kept near the shore and consequently in water which is contaminated. Oysters taken from these feeding grounds in rivers or inlets contain a much larger number of organisms than those directly from salt water away from the shore. If the oysters become infected, typhoid bacilli may live in them for some days, but there is no evidence that they multiply, and after a certain time they tend to die. There have been many investigations as to the distance at which bacteria may be found from the outlets of sewers. Thus Fuller found the colon bacillus in 40 per cent. of oysters and 70 per cent. of the samples of water taken five miles from a sewer outlet.

Dried fish have apparently carried the infection, as in a small epidemic in London in which many of those infected had eaten improperly cleaned fish from one shop.

(*c*) *Vegetables.*—These are carriers of infection only when eaten in the uncooked state. The danger of infection may be from the vegetables having been grown on land which has been fertilized by infected material, the water used in washing them may be infected, or the bacilli may be carried on the hands of those preparing or handling them.

4. Flies.—Much evidence has been brought forward to show that flies are frequent carriers of infection, and there is no question of the proof. They may carry the bacilli in one of two ways: the infected material may cling to the fly and be deposited on the food, or the bacilli may be swallowed by the fly and deposited later. Fischer estimates the duration of life of typhoid bacilli in the bodies of flies as twenty-three days. They can live for some days on the head and legs of flies.

Flies were important agents in the transmission of the disease during the Spanish-American War. They settled on infected fecal material

and later on the food. In camps, where lime had been used to disinfect the privy pits, flies with their feet covered with lime were seen walking over the food. The disease was less prevalent among regiments that had the mess tents screened. With the decrease in the autumn of the number of flies, the number of cases lessened, and this at a time when, as a rule, the disease is on the increase. In the South African War flies played a large part in the transmission of the disease.

Many of the instances of the spread of the disease in rural communities are due to flies. It is easy to understand how the dwellers in an ordinary farm-house can be infected, especially if the excreta are not carefully disinfected. The convalescent with bacilli in his urine may be an especial source of danger. Even under good sanitary conditions, and with disinfection, flies may carry infection, for it is often noted that certain typhoid fever patients attract flies, and it may be possible for them to pick up some bacilli, which are carried and infect food.

5. Dust.—This may be a factor under certain conditions. Typhoid bacilli soon die if desiccated, but if the interval be short they may survive. Thus in the South African War there were frequent dust-storms, so that the food was covered with dust and sand. Bacilli deposited on the surface of the soil could readily be carried and so infect food.

6. Clothing.—Under usual conditions of life, instances of infection being carried in this way are rare. Those handling soiled linen which has not been properly disinfected may contract the disease. It is, however, when men are crowded together, as in barracks or camps, that clothing is a common carrier of infection. This was especially brought out in the Spanish-American War, in which clothing, blankets, and tents became infected. Epidemics in barracks have been reported which seemed to be from infection of the clothing. The matter has an important bearing on the care with which we should disinfect the rooms and bedding used by typhoid fever patients. There is no doubt that typhoid bacilli can live for some time on clothing.

7. Conditions in the Soil.—Long regarded as the most important factors in the spread of the disease, and in fact considered an essential element, we now consider these as only influencing the difficulty which the bacillus may have in passing from one individual to another. Changes undergone by the bacillus in the soil are not necessary to enable it to become pathogenic. It is evident that conditions of drainage may determine infection, but this is mechanical and not due to any properties in the soil itself. There may be infection of certain areas, but the earth holds the bacillus in the same way as infected clothing might. The endemic character of the disease, especially in rural communities, may be largely due to local soil infection, and it has been shown that the bacilli may live for long periods in sewage-soaked earth.

8. Air.—It is difficult to prove that infection is ever carried by the air, except with dust, and it may be regarded as of very rare occurrence. The view that the breathing of noxious gases may be a means by which the disease is conveyed is not proved.

9. Carriers.—These may be divided into two groups: the primary, idiopathic, or contact carriers, and the secondary carriers. The

members of the first group are those who come in contact with typhoid patients, such as nurses and orderlies, but who, so far as known, have not had a definite attack of typhoid fever. One is strongly suspicious that many of these may have had a mild attack. The second group is composed of those who have had a frank attack and excrete typhoid bacilli after recovery. It is estimated that about 4 per cent. of those who have had typhoid fever become carriers for some period. In such cases the factors are present which protect the patient, but not those which lead to destruction of the bacilli; their immunity is not bactericidal or bacteriolytic. In the majority of these cases the bacilli pass out with the stools and the gall-bladder is probably the usual source. In a minority the bacilli are excreted in the urine. In some cases the bacilli disappear during convalescence and reappear some months later. The carriers are often recognized by investigations which follow the breaking out of epidemics. Usually the agglutinating power of the blood serum is increased in the carriers, which aids in recognition, but in some this is determined by a persistently high opsonic index. The bactericidal and bacteriolytic powers are below normal, and so the immunity is phagocytic and not bacteriolytic. Mild attacks are common in children, and as an example of this an instance is reported in which a child one and a half years old and nursing infected a number of people. The child was not especially ill, only showed mild diarrhœa, but the blood gave a Widal reaction and typhoid bacilli were obtained from the stool.

The Organism.—The *Bacillus typhosus*, discovered by Eberth in 1880 and grown in pure culture by Gaffky in 1884, is a motile, flagellated bacillus, 1 to 3μ in length and 0.5 to 0.8μ in diameter. The ends are rounded and it sometimes occurs in chains. Under certain conditions it forms "pseudofilaments." The size and morphology may vary with conditions of the culture media, age, etc. Flagella are often numerous. It does not form spores; the bodies seen at one or both ends of the bacillus and formerly regarded as spores are probably areas of degeneration. It is non-liquefying, non-aërogenic, aërobic, and optionally anaërobic, growing best at 37° C. The toxin belongs to the intracellular group. It stains by the ordinary method and readily gives up color to a solvent. It grows readily in various media, especially in bouillon and milk, and on gelatin, agar, blood serum, and potato. Motility is marked in certain media, especially bouillon. In the majority of instances it can be readily recognized in cultures. Its determination is aided by the specific agglutination reaction.

The organisms are usually killed by a temperature of 60°. They are very resistant to cold and can live for three months in ice, while repeated freezing and thawing does not necessarily kill them. In distilled water they may live for three months, but in ordinary water they usually disappear within from two to seven days. The duration of life in water is important, but it is not easy to say in any given water supply how long the bacilli may live. This apparently varies with the amount of movement, light, chemical substances, etc., as well as the number of saprophytic bacteria present. The more contaminated the water, the shorter time do the typhoid bacilli live. They have been reported as living for eighty

days in drinking water, but in reservoirs and dark wells they probably live much longer. In mud and the scrapings from wells they may exist for some weeks. They have been found in water-filters. In carbonated waters they can exist for weeks. In ordinary soils they seem to live for some months, and if bouillon be poured over the area they may live for a year, although in ordinary soil the bacillus usually disappears from the surface layers after a heavy rain. Under a leaking drain they have been found to live for two months. There is no evidence that they multiply in soil. They may resist drying; thus on cloth they have lived for nearly three months, while from cloth fouled by feces containing the bacilli they have been recovered seventeen days later. On thread kept under suitable conditions they may live a year. They have been obtained from the dust of soil which had been inoculated and then allowed to dry. The duration of life in feces is variable, depending on many factors, especially on the chemical character and the other bacilli present, but probably as a rule it is short, although some writers state that they may live for months in cold weather.

The *B. typhosus* belongs to a group of organisms which are similar in certain particulars. Of these the colon, paracolon, and paratyphoid bacillus, with the *B. enteritidis*, are the best-known examples. They may be regarded as forming a series with the colon bacillus at one end and the typhoid bacillus at the other. Cultural differences are usually enough to distinguish them. The intermediate group of organisms may be easy to distinguish from the colon or typhoid bacillus, but may resemble each other closely.

For many years, although the *B. typhosus* was constantly found in the bodies of those with the disease and could be grown in a specific manner, yet it had not been possible to reproduce the disease in animals. Grünbaum produced the disease in chimpanzees, 4 of which were infected; 2 died and the others were killed; characteristic lesions were found. Others have confirmed these results.

There are many problems connected with the serum reaction which require solution. Thus there are patients who do not give the agglutination reaction at any time or only late in the attack. This may be true of mild or severe infections. It may be that some of these are due to different strains, and it has been advised that in such the reaction should be tried with different varieties or a mixed bouillon culture be used. It has been suggested that bodies which prevent agglutination may appear and that there may be disintegration products. This may be avoided by using very dense mixed bouillon cultures.

In 1885 the bacilli were isolated from the blood by Fraenkel and Simmonds, but this was regarded as an unusual occurrence. The increased number of observations which showed the bacilli in various parts of the body suggested that they must occur frequently in the circulating blood. By using large amounts of blood and diluting it, positive results are obtained in a large percentage of cases. They are found most frequently in the early stages of the disease. Coleman and Buxton have collected the records of 604 cases, in 75 per cent. of which the bacilli were obtained from the blood. Of 85 cases in the first week bacilli were

obtained in 93 per cent.; of 198 in the second week, in 76 per cent.; of 115 in the third week, in 56 per cent.; and of 55 in the fourth week, in 33 per cent. Bacilli were found in the relapse in 18 out of 21 cases. They may be found in the blood at the time of post-typhoid chills. In all cases the bacilli are in the circulating blood at some period and this can be shown in nearly all patients by proper methods.

The bacilli are probably always present in the rose spots, and as regards the viscera and glands it may be said that practically every one may be invaded. Abscesses in the skin, subcutaneous tissues, muscles, or glands may contain them. In a percentage of the complications in the glands they are present in pure culture; for example, in the parotid and thyroid glands, and also the breast, testicle, ovary, and tubes. They may occur with suppuration or may be obtained by puncture without pus formation. In the lung they usually occur with other organisms, but may be found in pure culture. Not infrequently they occur in the sputum. In the liver they are usually present, and have been obtained in cultures from a liver abscess. In the spleen and mesenteric glands they are always and in the kidneys often present. In the circulatory system they are found in endocardial vegetations and in thrombi. They have been found in the sweat, but their occurrence in the urine is important. As a rule they are not found until later on in the disease, very rarely appearing until the third week, and in some patients they may not appear until convalescence. The frequency varies, but probably about 25 per cent. is a fair estimate. The number which may be present is enormous and billions of bacilli may be excreted each day. In the stools the bacilli are comparatively few. The persistence in the gall-bladder is important, as here they may be present for many years, and it is possible that they may be passed into the intestines and out with the feces. In certain parts of the body, such as the bones, they may be present for years in pure culture. The bacilli may gain access to the body without the individual having typhoid fever, and cause symptoms in a particular organ.

The typhoid bacillus may cause suppuration, but certain other organisms are often present with it, and it may be difficult to say which is primary and which secondary. The colon bacillus, streptococci and staphylococci, and others may be found, and obtained from the blood during life. At autopsy it is common to obtain many organisms, among the most common being the colon bacillus, streptococci, staphylococci, *B. proteus*, *B. lactis aërogenes*, the gas bacillus, and pneumococcus.

At autopsy the *B. typhosus* has been obtained from almost every part of the body. The bacilli are found most constantly in the spleen, mesenteric glands, and gall-bladder. In the alimentary tract they may be found in the mouth, especially in cultures from the tongue and tonsils, and frequently in the mucous membrane of the œsophagus. In the mucous membrane of the stomach, duodenum and jejunum, ileum and cecum, they are usually found; in the colon the frequency depends on the distribution of the lesions, while in the rectum they are rare.

Pathology.—External Appearance.—This varies greatly with the day of the disease on which death occurred. If early, as from severe toxemia,

the body is fairly well nourished and but little emaciated, while if late in the course there will be emaciation which may be extreme. The skin is usually very pale and there may be bed-sores. On section the muscles often show a characteristic change, having a curious, dry dark red color.

The Nervous System.—When we consider the frequency and severity of the nervous symptoms the changes found are comparatively slight. Meningitis[1] is rare and the lesions are of two kinds—one in which they are not of suppurative character (the so-called serous meningitis), and purulent meningitis. In the former group there are changes in the cerebrospinal fluid, with which changes in the meninges, consisting principally of œdema and hyperemia with round-cell infiltration, may be associated. In the purulent meningitis there is thickening of the meninges with a purulent exudate which is less on the surface than among the tissue-elements and between the meninges and the brain. In the arteries there are masses of cells which in places lift up the endothelium so as to block the lumen of the vessel. None of these changes are peculiar to typhoid meningitis.

The brain shows no characteristic lesions. In some cases round-cell accumulations have been described. Encephalitis and softening have occurred. Hemorrhage is exceedingly rare, while abscess is most likely to occur as a result of secondary infection. Gross changes in the cord are rare. There have been cases in which with an acute myelitis, typhoid bacilli have been found in the affected area at autopsy.

The Respiratory Tract.—Erosions may be found in the mucous membrane of the nose and occasionally membranous deposits in the nose, on the soft palate, and the tonsils. The mucous membrane of the larynx very frequently shows catarrhal inflammation which may have gone on to ulceration, having been reported in as many as 26 per cent. of certain series. The ulceration may be superficial but often extends deeply and involves the cartilages. With this there may be marked necrosis and formation of extensive abscess cavities. Ulcers on the epiglottis are fairly common; they are usually superficial but occasionally cause considerable destruction. Œdema of the glottis is rare. The ulceration may be due to decubitus or there may be superficial erosions which become infected and extend. In others it is probable that there is involvement of the lymph follicles comparable to that seen elsewhere in the body, and typhoid bacilli have been found in these lesions. Changes in the cartilages are sometimes primary and not due to extension. Baer found ulcers in the larynx in nearly 20 per cent. of 1109 cases. The trachea and bronchi do not usually show any marked changes. The mucous membrane is often reddened and may show a few small erosions. Ulcers in the trachea are very rare, Baer finding 3 among 529 cases.

The Lung.—Hypostatic pneumonia is comparatively rare and usually associated with cardiac weakness and a prolonged course. True lobar pneumonia is not especially rare. Horton-Smith reports it in 5 per cent. of his fatal cases and it was present in over 8 per cent. in the Munich statistics. It was found in 8 of 105 autopsies in this series. As a rule

[1] The cases in this series have been studied by MacCallum and Cole: *The Johns Hopkins Hospital Reports*, 1904, vol. xii.

due to the pneumococcus, in certain cases the typhoid bacillus is the causal organism. In others a mixed infection has been present. Bronchopneumonia is common and was found in 34 of this series. Gangrene of the lung is not very rare and may follow a lobar or an aspiration pneumonia. Abscess of the lung occurs rarely and in some instances the causal organism is the typhoid bacillus. Hemorrhagic infarction is comparatively common; the source of the embolus may be in the right heart or the peripheral veins. Infarction due to a detached clot from a thrombus is very rare but occurred in two of this series. The infarct may be gradually absorbed or abscess or gangrene follow. In one case there were areas of embolic pneumonia due to emboli formed by masses of phagocytic cells derived from the mesenteric glands.

Pleurisy is rare, especially the serous form. It occurred in only 3 of the autopsy cases apart from pneumonia. Empyema is also rare, although reported in nearly 2 per cent. of the Munich series. It was present in only one of this series. The organism in both serous and purulent pleurisies may be the typhoid bacillus.

Circulatory System.—The most important cardiac changes are in the myocardium. In the early stages the muscle shows comparatively little change, but later on some dilatation may be found and the muscle is flabby. This is by no means invariable, and the muscle may show but little change. On section it often has a curious yellow-brown (sometimes termed the dead leaf) color, and there may be quite marked mottling. Histologically there may be either interstitial inflammatory changes or marked parenchymatous degeneration. The muscle fibers may show marked vacuolation, with considerable deposit of pigment about the nuclei. With marked interstitial change there may be abundant round-cell infiltration. Changes in the small arteries of the myocardium have been described as an inflammatory hyperplasia. Endocarditis is extremely rare. There were but 11 instances in the Munich series and only 3 cases in this one. The typhoid bacillus has been grown from the vegetations, but in others there has been secondary infection. Pericarditis is also, and was present in one of this series.

The Arteries.—Involvement of the arteries, including the aorta, occurs more frequently than we have supposed. Fresh changes may be found in the intima of the aorta and coronary vessels. Thus in 52 cases of this series, in which full notes were made on the condition of the aorta, changes were present in 30, which were apparently recent in at least 21. There may be extensive areas of yellowish sclerosis, showing on section an acute process, which it seems proper to regard as having arisen during the course of the typhoid infection. Of the coronary arteries of 62 cases, in which the condition was noted, there were 19 with definite sclerotic changes and in 4 others yellow areas in the intima were noted. In 13 of these cases the changes were early and could be interpreted only as of recent origin. The general character of these changes may be common to infectious processes generally and not peculiar to typhoid fever, but it is important that the condition of all the arteries should be carefully studied in future autopsies. In some there may be arteritis with possibly thrombus formation.

The veins show changes more frequently than the arteries. Local thrombosis may be due to inflammatory change in the walls of the vein and in some cases is associated with the typhoid bacillus.

The Alimentary Tract. — Ulcers may be found in the pharynx (in 2.2 per cent. of Baer's 737 cases) but are more common in the œsophagus, as in 5 of this series. They were present in 4.5 per cent. of 223 cases collected by Baer. They may be part of the specific typhoid process or due to secondary infection. Œsophagitis was found in one case of this series. The stomach may show marked redness of the mucous membrane, and erosion or ulceration is not uncommon (2 per cent. of Baer's 1108 cases). Redness and swelling of the duodenum have been noted, but it is not proved that these lesions are specific. Seven cases of ulceration in the duodenum were reported by Louis and one by Andral.

Intestines.—On opening the abdominal cavity the intestines are frequently distended, this being usually most marked in the colon. The peritoneum covering the bowel may show a large number of hemorrhages. The areas on the outside of the intestine corresponding to the ulcers are deeply congested but show no granulation tissue formation, as in a tuberculous ulcer and are often very soft in their central parts, sometimes losing the dark red color and being rather grayish green, depending on the depth of the ulcer. The usual changes which occur in the bowel are most easily described in the four classical stages:

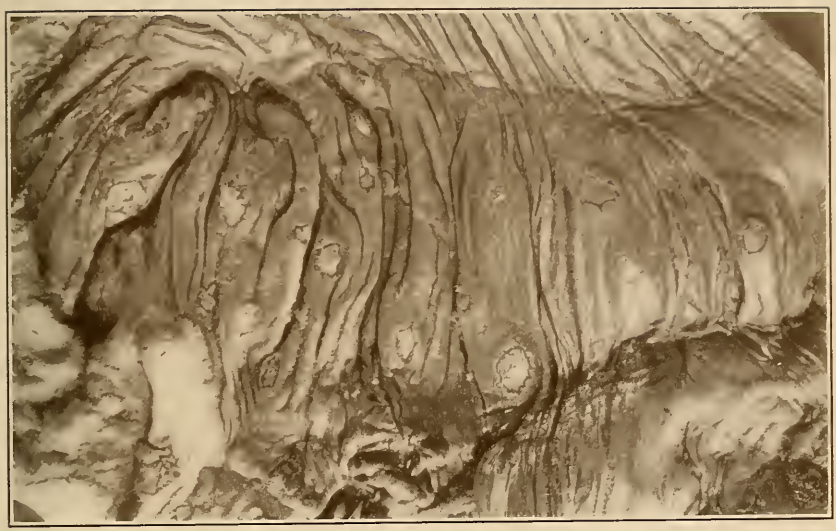
1. *Hyperemia and Hyperplasia.*—This involves the lymphoid tissue in the lower part of the jejunum, the ileum, and to a variable degree the appendix and the large intestine. The lymph follicles are swollen, grayish-white in color, and may project for some distance. The solitary glands may also be greatly swollen and are sometimes very prominent. There is nothing absolutely characteristic of typhoid fever in this hyperplasia, but it is rare to find such changes occurring with fever in any other disease in adults. In early life it may be very difficult to decide as to the nature of intestinal lesions by the gross appearance.

Microscopic examination shows a condition of marked hyperemia. There is a great increase in the number of cells, which may be so marked as to compress the smaller bloodvessels and give the grayish appearance so often seen. The cells are of various kinds. There is always a large number of ordinary lymphoid cells and also larger epithelial cells; some of these are phagocytic in character, and the swelling of the lymphoid tissue may be due almost entirely to their formation.

The number of areas which show hyperplasia varies greatly, for in some there may be only a very few infiltrated patches, while in others they may be so numerous that there is hardly an unaffected patch in the lower two-thirds of the ileum. As a rule the extent of the swelling is less in children than in adults. This process usually reaches its height from the eighth to the tenth day. Two modes of termination are possible, resolution or necrosis. The former is probably of much rarer occurrence than necrosis, but it is very difficult to know how often resolution occurs. The process is one of absorption and offers no special peculiarity; fatty changes occur in the cells, which are then gradually absorbed.

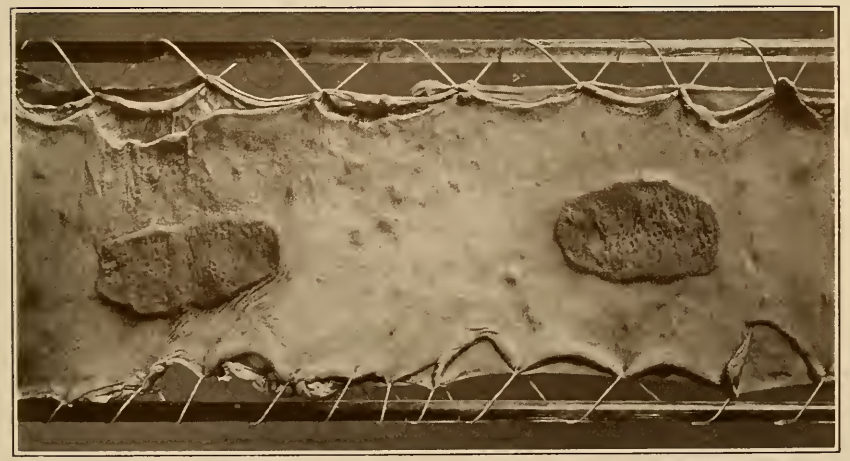
PLATE I

FIG. 1



Ulcers in the Colon.

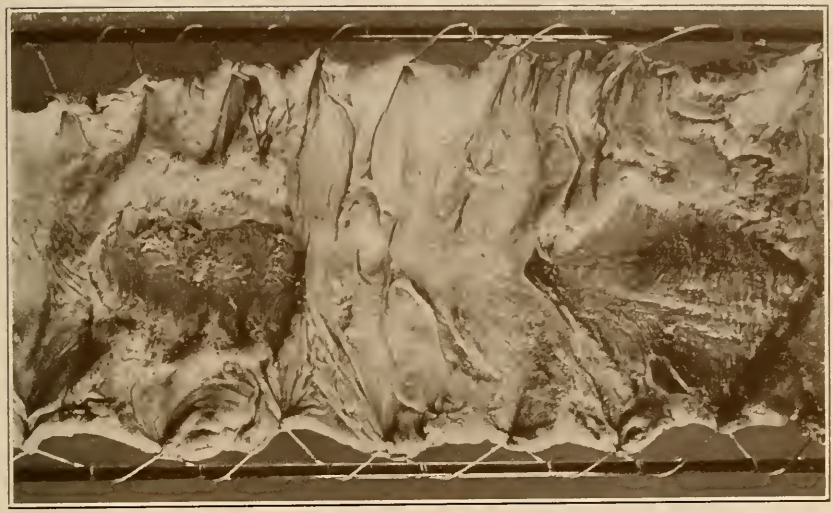
FIG. 2



Swelling of Peyer's Patches, with Slight Ulceration.

PLATE II

FIG. 1



Ulcers Beginning to Heal, with a Perforation in the Centre of the Larger One.

FIG. 2

Healing Ulcers.

The patches which are undergoing absorption show at first a grayish-yellow color and then gradually collapse—at first in the centre and from this toward the periphery—which often gives them a dotted or reticulated appearance. There is great variation in the extent of this process and in the coexistence of it with definite necrosis. We sometimes find the two side by side and with varying relative extent.

2. *Necrosis and Sloughing.*—This is probably due to several causes, as the diminished blood supply from pressure on the vessels and the presence of thrombi, as well as the action of toxins. The degeneration of the phagocytic cells beneath the endothelium of the vessel probably influences the formation of thrombi. Mallory has described this process also in the spleen and mesenteric glands. The extent of necrosis varies greatly; it may be superficial and involve only the mucosa or extend into the submucosa. As a rule the process is most marked low down in the ileum, and in some cases practically the whole lumen of the bowel for some distance above the ileocecal valve may be affected. In the colon the extent of necrosis is very variable, and in the solitary glands may involve only the most prominent part of a follicle. There may be every variation in the extent, number, and depth of the areas of necrosis.

3. *Ulceration.*—With necrosis fully established, separation gradually occurs, usually beginning at the edges and extending inward. The process does not usually advance equally throughout the whole area, so that the slough is rarely thrown off in one piece but as a number of smaller portions. In large ulcers, areas of ulceration and some still covered by slough may be seen. The ulcer left after this process varies greatly in extent and in depth. Some may be very slight—from 3 mm. to 2 cm. in diameter. The smaller ones usually result from changes in the solitary follicles, while the larger ulcers are usually on the site of the Peyer's patches. Adjoining ulcers may coalesce so that almost the whole surface of the bowel forms one large ulcer, as is especially likely to occur at the lower end of the ileum with the ileocecal valve involved in the process. The depth of the ulcers varies greatly. They may be superficial, with perhaps not the entire thickness of the mucosa involved, or the slough may extend down to the submucosa or the muscularis, which forms the floor of the ulcer in the majority of cases. It is usually considered that perforation occurs most frequently at the time of separation of the slough, while secondary ulceration may explain its recurrence at later periods.

The shape of the ulcer is very variable but they are usually more or less irregularly oval. While the long axis is usually parallel to that of the intestine, in some cases the opposite occurs, and annular ulcers involving the whole circumference of the bowel have occurred. The edge of the ulcer is usually sharp and for a time the margins may be quite steep in consequence of infiltration in the tissues about. The edges are usually soft, may be congested, and are sometimes undermined. Later the floor of the ulcer becomes comparatively clean and after a time shows a slate color. At this stage, when the lower ileum shows the characteristic ulcers, swollen and hyperemic Peyer's patches without any sloughing may be seen higher in the intestine.

4. *Cicatrization.*—This begins with the appearance of thin granulation tissue which covers the base of the ulcer. The mucosa gradually extends in and the epithelium forms over this. The glandular elements are apparently restored. After the process is completed the area is usually somewhat depressed and at first is of rather a lighter color. Subsequently there is usually the deposit of a certain amount of pigment. It is a question whether the lymphoid tissue is destroyed permanently in the areas of ulceration.

There may be combinations found in different parts of the intestine; healed and fresh ulcers may be found close together. With marked ulceration in the ileum the follicles in the colon may be swollen and show hemorrhagic areas without ulceration, or perhaps there is only one small ulcer in the large bowel, or many minute areas of ulceration. Very rarely is ulceration found in the large bowel alone. The *appendix* also shows much variation. Its mucous membrane may show no gross change, or there may be hemorrhagic areas or perhaps swelling with little ulceration. The colon may show a diphtheroid membrane.

Among the 105 autopsies of this series, in 4 there were no intestinal lesions; the site of ulceration in the others was: ileum 99, colon 59, appendix 15 (in 8 others the follicles were swollen but did not show ulceration), rectum 12, and cecum (with the rest of the large bowel free) 5. In 2 ulceration occurred only in the colon, in one the small intestine being perfectly free, in the other showing some injection.

Hemorrhage.—If this has occurred to any extent the bowel usually contains blood. If the bleeding has been from a large vessel this may be found in an ulcer with a large slough. It is sometimes possible to find the vessel from which the bleeding occurred. If the hemorrhage has been from capillaries or small vessels the areas may be found infiltrated with blood. In some ulcers the bleeding occurs at the edges.

Perforation.—The incidence of this may vary greatly in different epidemics and in different localities. Perforation was found in 30 of 105 autopsies in this series. It shows great variation in the time and situation, occurring more often in ulcers with adherent sloughs than in those which are clean. Perforation is in the lower part of the ileum in the majority; in only 5 of 32 cases with perforation in the ileum was the opening more than eighteen inches from the valve. The perforation may be in the appendix as in 3 of this series, or in the large bowel as in 4. The sigmoid flexure is comparatively often the site of perforation in the large bowel. In some cases perforation may occur in the rectum, and if this is low down an abscess may form in the perirectal tissues. There are cases of perforation in a Meckel's diverticulum and in the jejunum. Of the actual conditions which favor perforation we know little. Violent muscular movements may be a cause, but of the influence of peristalsis it is not possible to speak. Distension of the bowel may increase the chances of perforation but it is not possible to quote any figures which support this, or to say what is the relative influence of ulceration and other factors.

After perforation general peritonitis usually follows. There is much variation in the amount of fluid in the abdominal cavity but as a rule

it is considerable. Adhesions may keep the process localized and abscess results, the perforation being closed by the omentum or by adhesions. Peritonitis may occur without perforation and without any other evident etiological factor. Peritonitis may occur from perforation of the gall-bladder or from rupture of a suppurating mesenteric gland. There may be the accidental association of other conditions, such as an ordinary appendicitis, rupture of a gastric ulcer, or in women an extension from pelvic suppuration.

Mesenteric Glands.—These almost invariably show some involvement. In the early stages there is hyperemia and infiltration, with swelling. This probably begins about the same time as the infiltration of the lymphatic structures of the intestines. Their size varies very much, being often as large as a walnut and rarely the size of a small hen's egg. Areas of necrosis may be found, and as a rule the glands are soft and on section almost diffluent. Suppuration may occur with the formation of an abscess which may rupture into the peritoneum. Usually the glands about the lower end of the ileum are especially involved, but those higher in the abdomen may also show changes. The retro-peritoneal glands are often swollen and even the glands in the thorax and in the neck may be involved. Involution probably proceeds with the process in the intestine and the glands return to normal size.

Spleen.—The spleen is nearly always swollen at the beginning and during the course of the disease; the enlargement is usually moderate and the size is perhaps on an average about three times that of the normal organ. Very great enlargement of the spleen is not often seen. In 11 of this series the weight was over 600 grams, the greatest weight being 900 grams and the average 356 grams. The spleen is usually soft and may be almost liquid, so that it is difficult to make a section of it. In many cases it is very dark red and bloody on section. In 27 cases there were adhesions found, only 2 of these apparently being recent. Infarction and abscess may occur, but these were rare in this series (infarct in one case). Either an infarct or an abscess may rupture into the abdominal cavity and cause peritonitis. Rupture of the spleen has occurred, spontaneously or as the result of injury.

Sections made in the early stage of the disease show very marked hyperemia, with overdistension of the blood channels. Later on there is marked hyperplasia both of the splenic cells and of the stroma, and large numbers of phagocytic cells are found. Focal necroses are constant.

Liver and Bile Passages.—The liver early in the disease is usually hyperemic, firm and somewhat enlarged, but later it becomes paler and more friable. The structure of the lobules is usually not so evident on section. The most marked change is a parenchymatous degeneration, which may vary much in different parts. The liver cells at first are granular, turbid, and show fatty change, while after this they may contain granules and drops of fat and later on disintegrate. This process begins most commonly at the periphery of the lobule and is usually more marked here than at the centre. There may also be nodular areas, probably of two kinds, one being considered as lymphoid nodules, while the others are apparently necrotic. Mallory considers that there are

two varieties of these lesions; in one there are phagocytic cells in the lymph spaces and around the portal vessels; the second is due to the obstruction of the capillaries by phagocytic cells which have been carried by the portal circulation from their point of origin from the endothelium of the vessels of the intestine and spleen. Following this the liver cells lying between the capillaries undergo necrosis. These lesions are not peculiar to typhoid fever.

Abscess of the liver is extremely rare, there having been only 2 in this clinical series and 1 in the autopsy records. Acute yellow atrophy has been noted in connection with typhoid fever. Pylephlebitis is rare and is usually secondary to some condition in the peritoneum or mesenteric glands. The changes in the gall-bladder and bile passages are important. Ulcers in the gall-bladder offer no special peculiarities and may cause perforation just as in the intestine. Ulceration in the common bile duct is very rare. The influence of typhoid bacilli in the gall-bladder in favoring the subsequent formation of gallstones is thoroughly proved. Local infection of the gall-bladder without general infection occurs.

Pancreas.—Changes in this organ are usually not regarded as of importance. In the early stages of the disease the gland is enlarged and deep red in color. Histologically, dilatation of the vessels is found, with serous infiltration of the parenchyma.

Urinary Tract.—The kidneys are slightly enlarged, with a color redder than normal and hyperemic on section. As the disease progresses they may enlarge still further and have a yellowish tint. The histological changes are cloudy swelling with granular degeneration; this is usually seen first in the cortex and only later, and usually to a less degree, in the medulla. In certain cases there may be a definite acute nephritis, generally of an acute parenchymatous, hemorrhagic type which was found at autopsy in 8 of this series. Numerous small areas, infiltrated with round cells, which may pass on to suppuration, causing the so-called miliary abscess, have been described. These are probably usually due to micrococci but in some instances typhoid bacilli may be isolated from them. Lymphomatous nodules similar to those which occur in the liver have been noted. Multiple abscesses in the kidneys were found in 7 cases of this series. In the pelvis of the kidney and in the ureters small hemorrhages may be seen. Pyelitis is rare and was found in only one case. Diphtheritic inflammation of the pelvis may occur.

The bladder often shows hemorrhage into the mucous membrane. Catarrhal states occur not uncommonly and there may be also diphtheritic inflammation, which may cause a phlegmon. The occurrence of cystitis is not very common and only 4 were found at autopsy in this series. Abscess of the prostate was found in one of the series.

Histological Changes.—An important point in these is the absence of typical inflammatory lesions, except such as cholecystitis and meningitis. Special attention has been given to this subject by Mallory, whose conclusions may be summarized. The typhoid bacillus produces a mild toxin which causes proliferation of endothelial cells, epithelioid in character. These are produced (1) along the line of absorption from the intestine both in the lymphatics and bloodvessels, (2) through the general

circulation, especially where the circulation is slowest, and (3) throughout the body in the lymphatics by absorption of the toxin eliminated from the bloodvessels. These cells increase both in number and size and show marked phagocytic properties especially toward the lymphoid cells. This occurs especially in the lymph nodes and along the lymphatic vessels. This process is proliferative and may represent the extent of change in the solitary follicles in mild attacks. It may proceed further to disintegration of the phagocytic cells with fibrin formation, forming thrombi which block the lymphatic vessels. In the veins similar accumulations occur beneath the endothelium, probably in lymph spaces. By these and the resulting fibrin formation the vessels are occluded, and as the blood-supply is interfered with, necrosis results.

The changes in the mesenteric lymph nodes and spleen do not differ greatly, the increase in size being due to the proliferation of the phagocytic cells. In the liver, two varieties of focal lesions are found, one in the connective tissue around the portal vessels and therefore outside the lobule, the other in the lobule among the liver cells. The former consists of an increase of lymphoid and plasma cells, with the large cells derived from proliferation from endothelial cells. The lesions occurring in the lobule itself are due to the collection of cells from two sources, some being derived from the lining endothelium of the liver capillaries but the majority being carried by the blood current from the intestine and spleen. When a capillary becomes blocked by these large cells there is a process much like that found in the intestine, and other cells are added both by interference with the circulation and by division.

These large phagocytic cells may pass in the general circulation and cause focal lesions in the kidneys by occlusion of the veins of the pyramids. Similar changes may be found in the heart and testicle. The formation of thrombi, especially in the veins, may be due to a similar condition. The bone-marrow shows a condition much like that described in the intestine, lymph nodes, and spleen. There is congestion and œdema, with areas of necrosis and the presence of the large phagocytic cells. The blood-forming cells show general hyperplasia with a marked relative increase of the lymphoid over the granular cells. The myelocytes are decreased, agreeing with the diminished number of polymorphonuclears in the blood, and intercurrent infections do not alter this greatly. The eosinophiles are greatly diminished in number.

Mode of Infection.—The explanation of the exact mode of infection is still in doubt. Entrance by the tonsils has been suggested, which would make the infection primarily by way of the lymphatics and blood. Do the typhoid bacilli gain entrance to the body through a perfectly sound mucous membrane, or is a local lesion necessary? The instances of infection without intestinal lesions suggest that the bacilli may enter through a sound mucous membrane, but it is possible that minute lesions are not observed or have healed before the opportunity for examination. The finding of typhoid bacilli in the stools of apparently healthy individuals, and the fact that, of the total number of persons exposed to infection by the ingestion of typhoid bacilli, in only a certain number

does the disease develop, suggest that local conditions in the bowel may have an important influence. But there are so many possible factors that it is not safe to draw positive conclusions. The disease is primarily one of the lymphatic system. After the organisms have entered the lymphatics they multiply here and in the spleen. Some may enter the blood at an early stage. After the bacilli have multiplied two things occur, a number enter the blood and some are destroyed. The onset of symptoms probably coincides with this. After the response by the organism the destruction of the bacilli occurs more rapidly, more endotoxin is set free, and fewer bacilli enter the blood. Relapse is probably due to certain strains, against which sufficient protective bodies have not been formed, being able to multiply and cause symptoms.

Types of Infection. — Infection with the typhoid bacillus may be followed by different results, in one the typical disease, in another a local lesion, again a general infection without local lesions, or the brunt of the attack may fall on one organ. It has not been proved that there is any relationship between the severity of the disease and the number of bacilli found in the blood and the severity of the attack does not necessarily agree with the virulence of the bacillus. It has been pointed out that we must distinguish between the toxicity of the bacillus and its invasive capacity. The passage through animals probably diminishes the former but increases the latter. This goes to explain the fact that in many epidemics the invasive properties were marked but the toxic properties became weaker, which would account for the comparatively low death-rate in the Spanish-American War.

The forms of infection may be classed as follows:

1. *With the Usual Intestinal Lesions.*—This is the commonest form and includes the majority of cases.

2. *With Slight or Atypical Intestinal Lesions.*—This group is of uncertain frequency. Slight lesions in the bowel may be difficult to find and may be absent in the ileum but present in the colon or stomach. The lesions may have been without necrosis and entirely healed before death. The diagnosis is made by bacteriological findings.

3. *Cases without Intestinal Lesions.*—There were 4 such cases in the present series. There seems no question of their occurrence, although it may be difficult to say that slight lesions have not healed. The diagnosis can be made positively only by obtaining the bacilli.

4. *Local Infection.*—The importance and frequency of this is being more and more realized. Cholecystitis, meningitis, and encephalitis are examples. This form of infection is also not uncommon with organisms of the paratyphoid group. The number of these cases is regarded by some as large, but it must be remembered that to exclude the occurrence of a mild attack years ago may be impossible. Still we must recognize that these cases constitute a group by no means small.

5. *Terminal Infections.*—The typhoid bacillus has not usually been regarded as one which might cause a terminal infection, but in this series there were two such instances. Both were patients with malignant disease and both were without intestinal lesions. Typhoid bacilli were obtained from the blood during life.

6. "*Paratyphoid Infections.*"—It seems justifiable to include the various infections caused by organisms which, while closely related to the *B. typhosus,* are still distinct, under the general heading of typhoid fever. There were 8 of these in the last 500 cases of this series.

7. *Mixed Infections.*—In a certain number of cases, in addition to infection with the typhoid bacillus, another organism is added. This may be the colon bacillus, pneumococcus, streptococcus or staphylococcus. This may be early in the attack and coincident or occur as a secondary infection which is frequently a terminal one.

Symptoms.—Introduction.—The manifestations have an almost infinite variety; from the onset, throughout the course, in the termination and sequelæ we may expect anything. Not only is there great difference in the symptoms shown by different patients but the character of the disease in the same locality may vary greatly from year to year. Thus in one year the patients may have few rose spots while in the next the rash as a rule is very profuse, and the same may be seen in the occurrence of hemorrhage. This may be due to the character of the infecting organism. For the student it is most essential to realize that the classical description of the disease does not fit every patient and this makes it so important that the disease should be studied from the patient and not from text-books alone. No symptom or sign is necessarily present, a point never learned by some men who refuse to make the diagnosis of typhoid fever unless certain classical features are found.

Incubation.—The period of incubation may be impossible to determine exactly and it probably has limits varying from three to twenty-three days. In the instances reported by Dufloeq and Voisin, in which the patient swallowed a virulent culture of bacilli with suicidal intent, there was headache and malaise on the third day, fever on the fourth, epistaxis and rose spots on the eighth, and a palpable spleen on the ninth day. The report of the Spanish-American War Commission gives the average period of incubation, based on a study of 780 cases, as ten and one-half days, the shortest being slightly less than six days. The first symptoms are often so indefinite that no positive statement can be made as to the incubation period. At first the patient may feel out of sorts, be easily tired, and complain of general malaise without anything more. Probably the majority of patients have some symptoms during this period.

The Onset.—This may be very variable. The most frequent symptoms at onset in this series were as follows: headache 1117, anorexia 825, diarrhœa 516, abdominal pain 443, general malaise 436, vomiting 404, cough 393, chilly sensations 392, chill 334, epistaxis 323, fever 285, nausea 255, constipation 249, backache 215, sweating 207, general pains 196, weakness 112, delirium 65, dizziness 61, stiffness of the neck 47, sore throat 32, herpes 18, deafness 13, insomnia 11, photophobia 6, intestinal hemorrhage 4, convulsions 3, arthritis 3, syncope 3, jaundice 2, retention of urine 1, otitis media 1, hiccough 1, and bone lesions 1.

The most common features at onset are headache and anorexia. The headache is frequently severe and is often referred to the top of the head, while in others it is only a more or less general soreness. After these in frequency come diarrhœa and abdominal pain. To the former

much importance is given in the usual descriptions but in many patients it has followed the taking of a purgative. The less frequently purges are given early in the disease, the smaller will be the number of cases of diarrhœa. The occurrence of abdominal pain in nearly 30 per cent. is surprising and also important, as this may lead to error.

Of the general symptoms malaise was the most common, being found in 436. Chills and chilly sensations are comparatively common. The percentage with chills at the onset (22 per cent.) is high, especially as many writers consider that they are rare. General pains, backache, weakness, and dizziness occur in a certain number. Fever is not a common complaint of onset when we remember that it must be almost always present; sweating may be associated, although usually the skin is dry. The classical epistaxis was present in 325 or a little over 20 per cent. Herpes was comparatively rare and was found in 18 of the series or 1.2 per cent.; its infrequency is an important point to keep in mind in diagnosis. Atypical rashes have been reported but are not common.

The conditions which occurred rarely are of special interest as showing possibilities. Hemorrhage from the intestine may be the first symptom but this is, of course, not at the time of onset, although we use the term to mean the first symptom noted by the patient. In one patient whose first symptom was a bone lesion, it is possible that typhoid bacilli may have set up the local changes in the bone at the same time as the general infection was progressing. The first symptoms appreciated by the patient and the real beginning of the disease may be widely apart.

Special Modes of Onset.—While in the majority of cases the onset is slow and insidious yet it may be more or less sudden and with unusual features. The beginning may be with the ordinary symptoms in a very acute form or with marked symptoms in one system. The most common of these methods of onset are as follows:

1. *With Marked Nervous Manifestations.*—These are very various. The onset may be with convulsions as in 3 of the series. This is especially likely in children but may also occur in adults. In some instances there may be marked delirium or stupor and occasionally severe acute mania so that patients have been committed to an asylum. The disease may begin with symptoms which suggest meningitis, such as severe headache, delirium, retraction of the head, etc. Many of the symptoms of meningitis may be present without any organic changes in the membranes and in such the diagnosis may be made with great difficulty, although lumbar puncture is of much assistance. The early headache may be very severe, and if it be of a neuralgic type the diagnosis may be difficult. In some cases the attack is suggestive of influenza.

2. *With Marked Pulmonary Symptoms.*—There are instances of acute laryngitis but perhaps the most common condition is to find the initial bronchitis so severe that it quite overshadows the other features. This has often a very suggestive character; the cough may seem loose but there is little sputum. Again, the onset may be with an ordinary acute lobar pneumonia, the "pneumotyphoid" of the French. This has all the usual features and there may not be a suspicion that we are dealing with anything more than an acute lobar pneumonia. In some instances

the temperature may fall about the seventh day but soon rises again. The organism is usually the pneumococcus and very rarely the typhoid bacillus. This mode of onset may completely mislead the physician.

There is another lung condition sometimes found at onset which is difficult to diagnose definitely, as atypical signs and course are the most marked features. There is usually some distress and an increase in the respiration rate but the ordinary features of pneumonia are lacking. There is generally diminished expansion on the affected side, vocal fremitus is normal, possibly slightly increased or perhaps even lessened somewhat, there is moderate dulness, and on auscultation either suppression of the breath sounds or distant tubular breathing. In some cases the diagnosis of pleurisy has to be considered but the subsequent course and the negative results of punctures suggest that it is a "low variety" of pneumonia. In some, a small patch of distinct tubular breathing can be made out later on. The duration is indefinite, in some only a few days, in others lasting perhaps two weeks; it usually clears up slowly. This condition seems more frequent on the right than on the left side. It may give great difficulty in diagnosis if there be no positive signs of typhoid fever. Pleurisy at the onset may cause confusion, especially in case of effusion. In this series pleurisy at onset was rare.

In some patients the pulmonary symptoms may suggest tuberculosis. This is most likely if the patient has been feeling badly for some time and there are indefinite signs in the lungs. The possibility of the two diseases existing in the same patient has to be kept in mind.

3. *With Marked Gastro-intestinal Symptoms.*—Tonsillitis has been noted early in the attack but is rare. The onset may be with severe vomiting and marked abdominal pain so that some form of poisoning is suggested, but the vomiting usually does not persist. In others the diarrhœa may be so severe as to suggest an acute enteritis, especially if the stools have a watery character. In some the onset may be with gastric and intestinal disturbance accompanied by slight fever.

A deceptive method of onset is that with severe abdominal pain, as this leads to the diagnosis of an acute abdominal condition and it is by no means rare for such patients to be explored. The pain may be especially in the right iliac fossa with marked tenderness. If this has been of rather sudden onset the diagnosis of appendicitis is easily made. With pain in the upper abdomen, cholecystitis or some acute gastric condition may be suspected. An important point in the recognition is the fact that the abdominal pain of typhoid fever—except that due to complications—is much relieved by hot applications. The use of these and careful watching will, as a rule, prevent error or at any rate a needless exploration. Too much emphasis cannot be laid on the possibility of mistaking the abdominal pain which occurs early in typhoid fever for that due to appendicitis. The combination of pain, tenderness, rigidity, and muscle spasm is not found in typhoid fever apart from complications.

4. *Onset with Renal Symptoms.*—In rare cases there may be the features of acute nephritis—the "nephrotyphoid;" the urine may be scanty and contain albumin, tube casts, and blood. Retention of urine

is common at the onset and should rouse suspicion of typhoid fever in a doubtful febrile condition.

5. *Onset with Complications.*—In some instances there may be no suspicion of any illness, the patient only complaining of slight symptoms, until hemorrhage or perforation occurs. Four patients of this series were admitted with general peritonitis subsequent to perforation of a typhoid ulcer without any history of illness. In such patients it is only when the abdomen is opened that the condition may be recognized unless there happens to be a marked crop of rose spots. If by any chance the agglutination reaction is tried this may give the diagnosis.

6. *The Ambulatory Form of Onset.*—Under this term two different types of cases are described. Some writers use it to designate very mild attacks which are not severe enough to compel the patient to go to bed. As a rule, however, it is applied to the group composed of those who keep about and are at work having more or less fever. These are likely to have severe attacks and in hospital practice are well recognized as swelling the mortality. They supply a number of the instances in which the apparent onset is with marked nervous features.

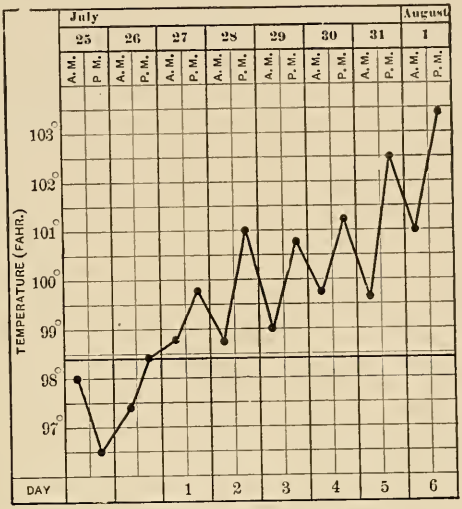
The *day of onset* may be difficult to determine. As a rule it may be considered as the day on which the patient gives up work or goes to bed. This is not always exact as there may be no question that the patient was ill for some days before he went to bed. In women or children there is often a history of their having to lie down for part of the day. This may be considered as part of the attack. Men frequently give up work for a day or two and then return to it until compelled to give up again. A striking feature is the change which may occur in the patient's condition after he has been put to bed, which is especially marked if he has been fighting the disease. A patient who has walked into the hospital may be almost unable to lift his head in two or three days. The temperature of the patient who has been at work or going about may not be high but after a few hours rest it rises rapidly. In hospitals, normal or even subnormal temperature records on admission are seen in patients who have walked some distance or had a long wait before admission. In such there may be a rise of four or six degrees within a few hours after they are put to bed.

The character of the early fever curve is of interest. While the step-like rise so often described (Fig. 1) is not uncommon yet in many instances the fever may attain a maximum by the third or fourth day. This is well shown in patients who for some reason have been in bed at the onset (Fig. 2). In the onset with marked symptoms in one organ the temperature may rise rapidly. The same may be observed in the onset of a relapse. This may be by a gradual increase in the temperature each day or it may rise suddenly from normal to 103° or 104° F.

As a rule by about the end of the first week the evening temperature reaches 102° to 104° F., by which time the appearance is often distinctive. The face is somewhat flushed, has an anxious look, and the eyes are bright. There is rarely any delirium at this stage but the patient may be easily confused and a certain mental slowness is frequently observed. This is especially noted when the history is being taken, the

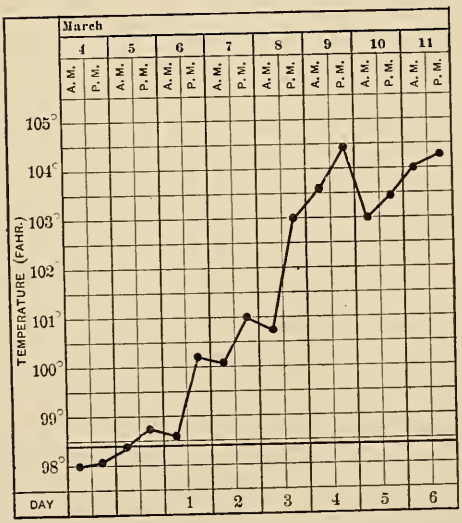
patient often having difficulty in remembering occurrences exactly and may have special trouble in giving times and dates. Some may show a little more confusion toward evening or at night. The tongue is very

FIG. 1



Onset with the patient in bed.

FIG. 2



Onset with the patient in bed.

often coated and white; the breath is frequently foul. The abdomen is sometimes distended and there may be slight gurgling and tenderness in the lower right quadrant. The bowels are often constipated, although there may be diarrhœa early in the course, especially if purgatives have

been taken. Bronchitis is common, often accompanied by a hacking cough but with little expectoration. The pulse-rate is usually low in proportion to the fever; thus a patient coming in with a temperature of 104° may have a pulse between 80 and 90. It is often full in volume, may be dicrotic, and the blood pressure is usually about normal. The spleen may be felt very early. The rose spots are rarely made out until the end of the first week.

Features of the Course.—In the second week of an ordinary attack the symptoms usually become more severe; the fever is higher, generally remaining fairly constant, and there is little remission either in the morning or after sponging or baths. The mental condition as a rule is dull and they will often lie quiet, paying little attention to what is going on about them and dozing most of the time. They can usually be aroused and will answer questions apparently perfectly correctly, but, to any one who knows the circumstances, quite incorrectly. One curious disturbance is the loss of definite ideas of time. It is important to remember this, because a patient who is apparently perfectly rational may state that he has received no nourishment for twenty-four hours, when perhaps not as many minutes have elapsed since his last feeding. Nurses are often subjected to unfair criticisms on account of these statements, and their unreliability should be kept in mind. In such cases it is well to explain the matter to the friends. The facial appearance usually changes during the second week, the early flush disappears, and they have a heavy, dull look. The lips are dry, the tongue is coated, and in severe cases is heavily furred. The breath is foul. There may be sordes on the lips and teeth if the attack be a severe one. The abdominal symptoms usually become more marked, there is a greater tendency to distension, and diarrhœa may appear or become aggravated. At this time or later there may be some complaint of abdominal pain. As a rule the bronchitis has subsided. The pulse usually becomes more rapid, probably is dicrotic, shows the soft quality so often present in typhoid fever, and the blood pressure may fall slightly.

Death may occur during this week, usually toward the end, and generally from profound toxemia, although both hemorrhage and perforation may occur. In mild attacks the temperature may have begun to fall and be about normal at the end of this week.

In the third week the conditions of the second week are aggravated or there are signs of the attack coming to an end. If it be a severe one the emaciation now becomes noticeable, the weakness is more marked, and the whole appearance of the patient is changed. The mental condition may continue dull; there may be a muttering delirium and muscular tremor in the severe cases. The tongue is often dry, tremulous, and protruded with difficulty; it may be swollen, fissured, and heavily furred. The abdominal symptoms may be more marked and diarrhœa or distension appear for the first time. The pulse rate usually increases, varying perhaps from 120 to 140 in severe cases. The heart sounds usually show changes, the first very often becomes feeble and indefinite and may almost disappear at the apex; the second is very often short and sharp. In others there may be embryocardia. The pulse is usually

small, very soft, and the blood pressure low, averaging perhaps 100 mm. Hg. Lung complications may occur, either lobar pneumonia or a hypostatic condition. Distension, hemorrhage, and perforation may occur. The back may show signs of irritation and bed-sores appear.

If the attack be milder, toward the end of this week the temperature begins to come down, both the morning remissions and those after the baths being more marked. The mental condition improves, the tongue cleans, and all the symptoms show improvement.

In the fourth week in the ordinary attack convalescence begins. The temperature gradually declines, the whole condition improves, and the appetite returns. In many cases, however, while the temperature comes down it does not reach normal and may remain about 100° F. In severe cases the condition may be an aggravated repetition of that in the third week. The mental state is worse, the patient lies oblivious to his surroundings and perhaps in a muttering delirium. There may be much muscular tremor and subsultus tendinum. In this condition involuntary passage of the urine and feces and retention of urine are common. The pulse usually becomes more rapid, reaching perhaps 140; it is small and the blood pressure may be lower than before. The abdomen is often distended and there may be diarrhœa. In such a condition there is often great difficulty in making the patient take sufficient nourishment and water. During this time there is danger of pulmonary complications, and hypostatic pneumonia may occur. Bed-sores have to be guarded against. In the following week severe cases may show continued fever with all the features spoken of in the fourth week, but as a rule there are signs that the attack is drawing to a close. The fever becomes more irregular, although it may come down to perhaps 100° or 101° F. and then remain persistently about the same figure. At this time relapses and recrudescences may occur and the patients are subject to some of the later complications.

Attacks of collapse may occur with a sudden drop of temperature, even to subnormal, and signs of severe shock. There is cyanosis, the respirations are shallow and rapid, the pulse is small, and there may be vomiting and diarrhœa. The abdomen is negative. The patient may die or gradually improve.

While general descriptions may be given, there is no account that can fit all cases. The general features may be mild and severe complications appear or toxemia may be marked and continue with high fever but without other special features. The early part of the attack may be mild and the temperature show signs of coming down when suddenly all the symptoms become worse and the patient passes into a serious state. In others the temperature may have come down but the toxemia and prostration continue.

General Appearance.—The aspect early in the disease is frequently very characteristic. The face may be somewhat flushed and the eyes bright, but with this there is a curious dull appearance more easily recognized than described and which in certain cases makes one suspicious of the diagnosis. The patients will often go into a doze during the examination and usually pay little attention to what is going on around

them. In the beginning of the second week the expression usually becomes duller and toward its end the patients lie with a listless heavy look. There are, however, patients of an acute nervous type who are very alert and whose senses, especially hearing, seem keener than normal. Toward the latter end of the disease the color usually leaves the face and is replaced by a pale, sallow look not necessarily associated with anemia. During convalescence after a severe attack the appearance is often characteristic, as the emaciation, with the falling out or thinning of the hair, gives a curious aspect.

Fever.—This may be regarded as a constant feature of the disease. The average duration in this series was thirty-one days. In 1118 the temperature reached 104° F. or over, in 643 the maximum was from 104° to 105° F., in 411 from 105° to 106°, in 58 from 106° to 107° F., and in 6 over 107° F. In only 25 per cent. did the temperature remain below 104° F. throughout the attack. The classical description of the fever of onset is of a gradual step-like rise, the temperature each evening being higher than on the preceding one but usually lower in the mornings than in the evenings. This is not constant and in some instances the elevation may be rapid. The fever, as a rule, reaches its height from about the seventh to the tenth day and then persists in a fairly steady line. But there is no constant rule and we see every variety of temperature chart. Toward the end of the attack, and especially in the third week in ordinary cases, the temperature begins to show remissions. The remissions are at first in the morning and for many days the temperature may go above 102° F. only in the afternoon. The termination is rarely by crisis as in two of this series.

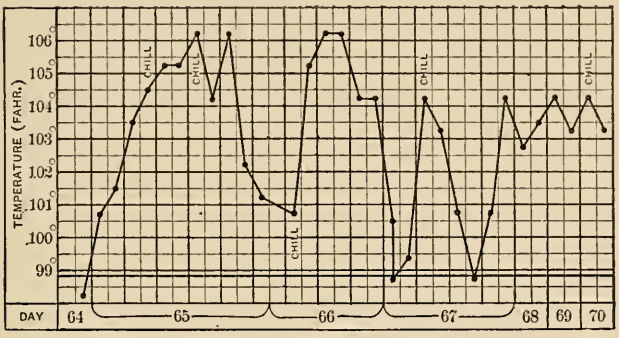
The temperature curve may show many variations. At times it may fall to normal and remain so for as long as twelve hours. This may occur early and is worthy of note, as in a doubtful case with fever for some days such a record would seem to rule out typhoid fever. Such mistakes make one cautious in attaching too much importance to such a drop. An inverse type of fever, higher in the morning than in the evening, is said to be common in patients who work during the night and sleep in the day.

Sudden changes in temperature may occur. These should always suggest the possibility of some complication but they are frequently seen without any cause being found. With the baths there may be marked falls in temperature which as a rule do not last long. With hemorrhage there is usually some drop in temperature which may be ten degrees. A sudden fall is not characteristic of perforation, although it may occur, but just as frequently there is elevation for a few hours which may be followed by a drop. In the latter part of the attack there may be marked variations. Hyperpyrexia is not common. The temperature rose above 106° F. in 64 out of the 1500 cases and above 107° in 6. Just before death the temperature may rise to 108° or 110° F.

The fever of the relapse may be practically a repetition of that in the original attack with the same gradual step-like ascent but in some the temperature may rise rapidly (Fig. 3). This is especially likely if the onset of the relapse is with a chill or with some complication. The

duration of the fever in the relapse is usually shorter than in the original attack. The fever of the recrudescence is of short duration and rarely rises very high, 101° or 102° F. being the maximum.

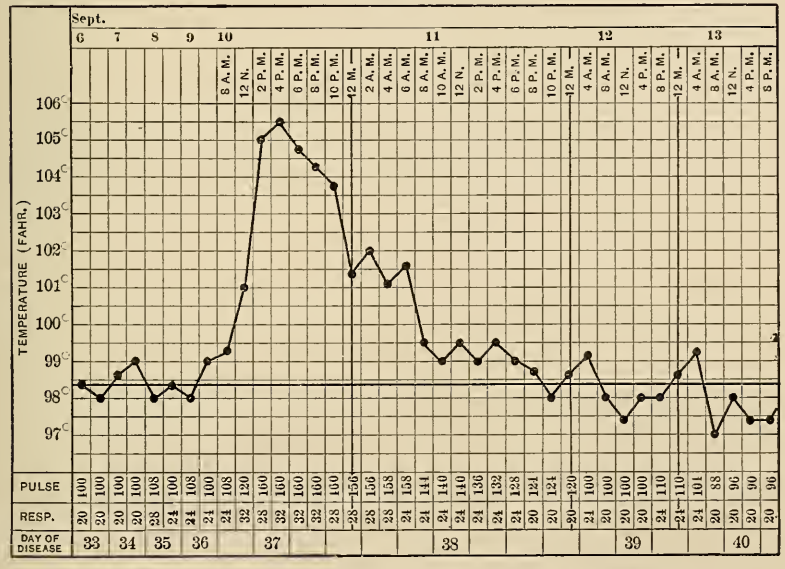
FIG. 3



Sudden onset of relapse with chills.

The temperature curve in convalescence may show two variations, one a slight persistent fever and the other a subnormal temperature. The slight fever, averaging from 99° to 100° F., is often very trouble-

FIG. 4



Elevation of temperature and rapid pulse in convalescence due to the eating of fruit.

some, as it may last for weeks, sometimes with the patient steadily improving, at other times with the condition almost stationary. Such fever always demands frequent careful examination to exclude a complication. Pleurisy, a slight phlebitis, or a bone lesion may be the explana-

tion. Constipation is sometimes a cause and many of these patients have a heavily furred tongue. In others too early an increase in diet is the cause of the fever, as can be shown by going back to liquid food. In others it may be due to a nervous condition or to anemia. In children this slight fever is more common and of less significance. If a complication can be excluded, the patient's general condition be good and the tongue clean, it is often well to either discontinue the taking of the temperature or take it only once or twice a day.

Hypothermia in convalescence is quite common. For days the temperature may not rise above 97° F. This is seen especially after protracted attacks or when there has been great emaciation. It usually does not persist for more than two weeks and is of no special significance. It was present in 168 out of 585 cases (28 per cent.) which were specially studied in reference to this point.

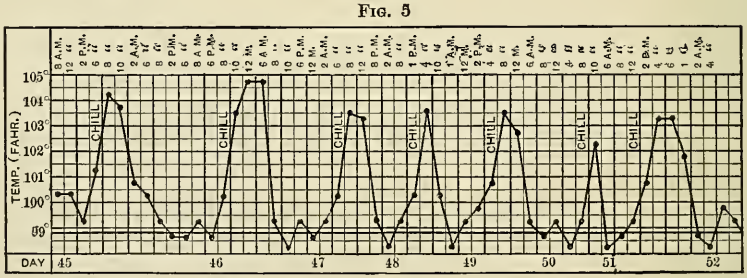
Post-typhoid elevations are by no means uncommon and may occur at any stage of convalescence. They were present in 92 of this series. They cause anxiety, as one always fears a complication. They may be accompanied by chills but as a rule the only feature is the sudden sharp rise of temperature which may be to 104° or 105° F. It may fall to normal in a few hours or may persist longer, though rarely more than twenty-four hours. It may be impossible to find any cause; phlebitis, excitement, or the eating of solid food may be factors (Fig 4).

Chills.—These are not infrequent and occur under various conditions:

1. *At Onset.*—This was the case in 334 of this series and often gives much difficulty in diagnosis, especially in a district where malarial fever is common. They may also occur at the onset of a relapse.

2. *With Complications.*—This may be at the onset of pneumonia, pleurisy, otitis media, perforation, hemorrhage, phlebitis, periostitis, suppuration, etc. It is this which makes the occurrence of a chill during the course always a disturbing matter. They may occur in instances of "septic infection." A chill may occur with hyperpyrexia sometimes without explanation.

FIG. 5

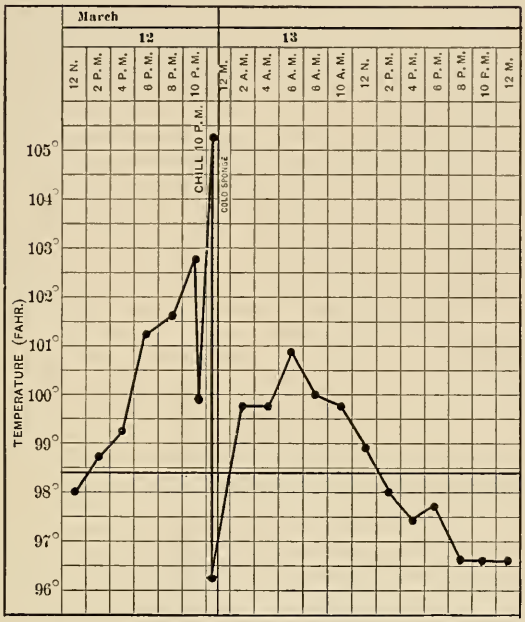


Recurring chills late in the attack.

3. *In Convalescence without any Complication* (Fig. 5).—It is difficult to give the cause in the majority of these. There may be repeated chills with high elevation of temperature. In several cases of this series at the time of each chill typhoid bacilli were obtained in blood cultures (Fig. 6) and colon bacilli in others.

4. *With Treatment by the Antipyretic Drugs.*—This is not rare, especially if the coal-tar products are given.

FIG. 6



Chill during convalescence associated with typhoid bacilli in the blood.

5. In some cases they occur at intervals through the entire course, perhaps with profuse sweating, and no explanation is found.

6. During convalescence they may occur in the rare instances of combined infection with typhoid and malarial fevers.

7. After the injection of serum or vaccines.

The chills may be very severe and profuse sweating may follow. Their occurrence should always suggest a careful examination for a possible complication. In some they are due to a secondary infection.

THE SKIN.—The skin manifestations are especially important for diagnosis. The characteristic rash appears in the form of small, rounded circumscribed red areas, termed the roseola or rose spots. They are slightly raised, of a pale red color at first, later becoming darker. They can usually be felt by the finger, disappear on pressure, and as a rule are discrete, although in rare instances they coalesce. The diameter averages from 2 to 4 mm. They usually appear from the seventh to the tenth day and are rarely seen at the beginning of the attack. They generally come out in successive crops, and after a few days, usually three to five, fade away, not infrequently leaving behind a faint brownish stain. The rash is very variable in its time of appearance, duration, and extent. It may not appear until late in the attack or even after the temperature has become normal, as in 21 cases of this series. The longest interval between the beginning of apyrexia and the first appear-

ance of the rash was fourteen days. Occasionally the rash may not be present in the original attack but appears in the relapse as in 3 cases of this series. The length of time during which successive crops may appear is variable. There may be only a few spots at one time or there may be an abundant eruption throughout the whole course of a long attack. In some patients with the rose spots present during pyrexia, fresh ones may continue to appear after the temperature is normal. The number of spots is also very variable. In some only 3 or 4 may be found during the attack or they may be present in large numbers. Perhaps 10 to 20 may be given as the average number present at one time but they may be very numerous, even 200 or more. The position of the spots shows considerable variation. As a rule they are most abundant on the abdomen and lower thorax but are not uncommon on the back and should be carefully looked for there if none are found on the front of the body. In some they may be seen on the neck and face, on the arms and hands, or on the legs. They may be found only on the arms and about the thorax.

There is rarely much difficulty in the recognition of typical rose spots but at times there may be some question as to the nature of suspicious spots. It is helpful to mark them so that they can be observed on succeeding days. Similar spots may be found with trichinosis and have been reported in acute miliary tuberculosis, but with these diseases they apparently do not come out in successive crops. An atypical typhus fever rash may much resemble that of typhoid fever. Insect bites should not be mistaken as they usually show a central point of hemorrhage. Acne-like spots may give difficulty.

Rose spots were present in 1205 of this series (80 per cent.). This included both white and colored patients; among the 1233 white patients they were found in 1150 (93.2 per cent.) while among the 267 colored patients they were found in 55 (20.6 per cent.). In the very dark colored patients it is not often possible to recognize them but they can be seen in those with lighter skins as darker areas on the surface. Palpation is sometimes an aid in their recognition. The rash was noted as exceptionally profuse in 164 patients. Of these it was on the arms in 81, forearms in 17, hands in 3, thighs in 43, legs in 15, about the knees in 3, ankles in 1, feet in 2, shoulders in 9, axilla in 1, neck in 6, face in 5, and on the scalp in 2.

In some patients the rose spots are capped by small vesicles and subsequently scabs may form over these. Some writers describe "pustular rose spots." In a certain number purpuric spots appear, as in 38 of this series. The rose spots may become purpuric or may be hemorrhagic on the first appearance, apart from those seen in the hemorrhagic type. Toward the latter part of the attack there may be quite marked *desquamation*. It may be marked over the abdomen even when no local application, such as turpentine stupes, has been used.

Among other skin lesions in typhoid fever the following may be noted:

1. *Erythema.*—It is not uncommon to find areas of erythema early in the disease, especially about the joints. It is of no special significance although in rare instances it may give difficulty in diagnosis. It was

present during the course in 15 of this series. If drugs, such as quinine, are given, erythema may be more frequent. Erythema nodosum may be present; in one patient it appeared at the onset. Erythema multiforme has been reported. Ecthyma was present in one patient of this series, who possibly had congenital syphilis.

2. *Urticaria.*—This occurs rarely and is more likely to be present when drugs are given. It was noted in only 2 of this series.

3. *Hemorrhagic Rash.*—Some variety of this is not uncommon. In 38 cases purpuric spots were noted; in the majority of these, typical rose spots first appeared which later became hemorrhagic. In 9 cases the rash was regarded as hemorrhagic, 3 of these being the hemorrhagic type of the disease. In severe cases ecchymoses may appear, especially in the dependent parts.

4. *Herpes.*—This is rare, especially in comparison with its frequency in various other febrile affections. It was noted in 20 cases of this series, of which 18 were at the onset. As a rule herpes appears in the first week and is on the lips, but it has been reported elsewhere on the body.

5. *Pemphigoid Rash.*—This was noted in one case.

6. *Peliomata or Taches Bleuâtres.*—These are bluish-gray subcuticular areas from 4 to 10 mm. in diameter, situated most commonly on the lower abdomen, the pubic region, and upper thighs. For a long time considered as almost specific evidence of the disease it is established that they are due to pediculi and not peculiar to typhoid fever.

7. *Miliary Eruption.*—This occurs fairly frequently in the form of round vesicles usually about the size of the head of a pin and occasionally showing coalescence. If profuse the rash gives a very striking appearance. No special significance is to be attached to its occurrence. As a rule it is most marked on the abdomen and sometimes on the chest.

8. *Ulcers.*—In a few instances, especially in children, these may be multiple, varying in diameter from 3 to 10 mm.

9. *Gangrene.*—This may occur in special epidemics but as a rule is a rare complication. There may be multiple areas of superficial gangrene of the skin and in children noma may occur. It occasionally happens that a small area of superficial gangrene occurs on the abdomen if an ice-bag has been applied for a long time.

10. *Furuncles.*—These are troublesome and by no means rare. Their most frequent situation is on the back and about the shoulder and gluteal region, although they may be found anywhere. They may be present during the fever, especially in protracted attacks, but are most likely to appear in convalescence. As a rule more troublesome than dangerous, yet they cause great suffering and in debilitated individuals prolong convalescence. While rarely the cause of death, yet in some cases they are the source of a terminal general infection. The organism found in the boils is usually either a streptococcus or a staphylococcus. The typhoid bacillus was not found in any of this series.

11. *Abscesses.*—These may occur during the attack but are more frequent toward the latter part of the illness and during early convalescence. They are sometimes responsible for elevations of temperature.

The character and size of the abscess may vary greatly. There are some which are small and superficial and much like boils, not uncommon in the perirectal tissues.

12. *Bed-sores.*—Their frequency has steadily diminished with better care and nursing. As a rule they occur in the sacral regions but in rare cases may occur on the heel, in the scapular region, or about the elbow. They are less common under the bath treatment. Incontinence of urine or feces strongly predisposes to their development. The physician should make it a part of his routine examination to examine the back. There are different kinds of bed-sores. The commonest is that which occurs in the sacral region. The skin shows a little redness, then there is some loss of superficial tissue with discoloration beneath, and usually after this a line of demarcation appears followed by the separation of a central slough. The amount of damage is very variable; only the skin and subcutaneous tissue may be involved or the process may go much deeper. It often happens that sound skin has been undermined and much more destruction has occurred than appears on the surface. Another type, termed by Curschmann the subcutaneous one, does not always develop in areas subjected to the greatest pressure. As a rule the process begins in the subcutaneous tissues, the skin gradually becomes discolored, softening goes on, and finally there is the discharge of dirty, often sanious, pus. There may be several discharging sinuses and in such cases there may be destruction of a large amount of tissue and the necrosis extends to the bone. This is especially likely to occur in the profoundly toxic patients. It is doubtful in certain patients if any care can prevent the development of this form of bed-sores and it seems well to emphasize this, as the statement that the nurse is always to blame when a bed-sore develops is not true.

13. *Lineæ Atrophicæ.*—These may appear very abundantly, as after any acute illness. They are especially frequent over the lower abdomen and thighs but may be seen about the shoulders or knees. Certain cases may be due to neuritis.

14. *Hair and Nails.*—It is common for the hair to fall out after the attack. This seems less likely to occur if it has been cut short at the beginning of the illness. If the hair has been lost the new growth takes place slowly. Permanent baldness has occurred but is rare. The nail usually shows a marked groove which appears as the nail grows out.

15. *Odor.*—In some patients there is a very characteristic odor which is often described as mousy or having a musty quality. It is sometimes most noticeable in the palms of the hands. Under active hydrotherapy it is probably less frequent but seems to be a peculiarity of certain patients and may be present during the attack and well into convalescence.

16. *Sweating.*—This is not common at the onset, especially if there be chills or chilly sensation. During the course it is rare except with some of the complications. With hemorrhage or perforation the patient may sweat most profusely. In convalescence it may occur with the post-typhoid chills.

17. *Pigmentation of the Hands and Feet.*—In some patients there is a marked yellow color of the palms of the hands and soles of the feet,

usually most marked toward the latter part of the attack. It has no significance.

The Digestive System.—The mouth usually shows certain changes. There is a tendency to dryness and often some swelling of the tongue which shows indentations of the teeth. The tongue is usually coated with a white fur which later on may become very thick. In severe cases the tongue becomes dry, covered with a dark fur, and may show fissures which bleed readily. The teeth may be covered by sordes and also the lips, which may be cracked and bleed. With the giving of large amounts of water internally, and regular attention to the mouth, the tongue may remain moist and only lightly coated, while the lips remain practically normal. The condition of the mouth is a good index of the care which the patient is receiving. In very severe attacks when the care of the mouth has been neglected, thrush may develop. A diphtheroid membrane may be found. Stomatitis occurs occasionally and ulceration of the mouth and circumscribed gangrene have been noted. Noma occurs rarely, usually in children.

Acute Glossitis.—This is rare and occurred only once in this series at the onset of a relapse. This complication is not likely to be serious, as the swelling can be readily diminished by incision into the tongue or by drawing blood from it by a needle.

Parotitis.—This is an important complication which occurred in 14 of this series (0.9 per cent.), which is about the frequency found in larger statistics. Among 12,173 cases (London Fever Hospitals, Hoffmann, J. McCrae and the present series) it occurred in 93 (0.7 per cent.). It is thought to have become rarer in recent years owing to the greater care given to the mouth. It is more likely to occur in severe attacks. The infection may be by direct extension along the duct from the mouth or through the blood. It may be part of a general infection, a general infection may follow it, or serious intracranial complications, such as thrombosis, may result. It usually appears in the third week or later, and in some instances during convalescence. The clinical features do not differ from secondary parotitis under other conditions and as a rule it is unilateral. If both parotids are involved one usually follows the other. The swelling appears first behind the angle of the jaw and may increase very rapidly. The skin over it is usually red and there is marked induration and tenderness. There may be a chill with the onset and the temperature usually becomes higher. There is generally severe pain. The course is variable and in some the swelling subsides but in others suppuration or gangrene occurs. Early incision is advisable if there are any signs of suppuration. Marked necrosis is found in some and the greater part of the gland may slough away. There are instances of extension of the process to the structures of the neck, even to the mediastinum.

The organism present is usually either the streptococcus or staphylococcus. The typhoid bacillus may be associated with these or found in pure culture. In some cases on early incision no pus is found but coverslips and cultures show large numbers of streptococci. Typhoid bacilli were not obtained in any of this series.

The condition is serious. Death occurred in 5 among 14 cases in this series and the mortality of reported cases is about 30 per cent. This is partly due to the occurrence of parotitis in severe attacks. After recovery there may be persistent enlargement and induration of the gland. In some instances there may be deformity and facial paralysis has been noted. In one of this series persistent sweating in the parotid region, during eating, followed an abscess.

Submaxillary Glands.—These may show involvement as in 4 patients of this series, of whom 3 died. Streptococci were found in 2 and typhoid bacilli and staphylococci in 1. In 1 a marked angina followed and in 1 both glands were involved.

The Pharynx.—Involvement of this is rare. Early in the disease there may be slight inflammation with congestion, or membranous pharyngitis may appear later. Usually in severe cases the pharynx shares in the dryness of the mouth and may then be covered with a very tough mucus which the patient is unable to cough up and which often gives a great deal of discomfort. There are instances of ulceration of the palate, tonsils, and pharynx, which may occur early in the attack, and in 3 out of 4 such cases reported by Marquordt from Ebstein's clinic, typhoid bacilli were obtained. Probably they would be more frequently noted if routine examinations of the pharynx were made with more care. Hemorrhage has occurred from the tonsil.

Angina.—This is exceedingly rare and may extend from lesions in the pharynx or from a submaxillary gland. The swelling may be extreme, it is apt to have a boggy resistant feel, and there may be some interference with respiration. The only instance in this series was a young adult who died suddenly without any signs of obstruction. There were numerous small foci of suppuration through the structures of the neck.

The Œsophagus.—Lesions here are rare and were considered to be more important by Louis (who found ulcers in 7 among 46 cases) than perhaps by any subsequent writer. In the autopsy records of 2544 cases (Munich, Ouskow, and the present series) ulcers were found in the œsophagus in 4. They were present in 3 of 105 autopsies in this series. Typhoid bacilli have been found in the ulcers, but in others they are due to secondary infection. Their presence may be suspected when the patient seems to suffer pain when swallowing. Hematemesis may occur. Œsophagismus has been reported without any cause being found at autopsy. Superficial erosions have been found at autopsy, but it is doubtful if they cause any symptoms. In 2 of this series a diphtheroid membrane was found and in 1 there was an acute œsophagitis with hemorrhagic areas and much destruction of the mucosa.

Stricture of the œsophagus is one of the rare sequels. There was one instance in this series. Several cases are reported, the history usually being of difficulty in swallowing coming on during convalescence and first noted when solid food was taken.

The Stomach.—As a rule gastric disturbances are not common. At the onset there may be nausea and vomiting, especially in children, but these rarely persist, although protracted vomiting occurs occasionally.

Sometimes gastric distress is complained of without either severe pain or vomiting. Hiccough is rare and generally associated with a complication, especially perforation. During the height of the disease vomiting occurs so seldom that we regard it as suggestive of a complication. It may be from improper feeding, too much water, or the giving of drugs. Occasionally it is due to ulcer of the stomach from which bleeding may occur and erosions may be found at autopsy from which it is possible that there has been oozing. Hematemesis occurred in 4 of this series. An ordinary round ulcer may be present and in one patient death was due to hemorrhage from it. Perforation of a typhoid ulcer in the stomach has occurred. In convalescence, dietetic errors may be responsible for nausea and vomiting. There may be marked distension of the stomach with gas, often with intestinal meteorism, which may interfere with breathing. Acute dilatation of the stomach occurred as a terminal event in one patient.

As a rule there is complete loss of appetite, usually from the onset as in 825 of this series, and almost invariably during the course. In some instances the patient may have a fair appetite throughout the whole attack or even be extremely hungry.

Intestines.—The intestinal features may vary greatly from year to year, but it should always be kept in mind that disturbances may be due to meddling. The less interference there is with the bowels the less trouble there will be with them. During the course of the disease the bowels were regular in 465 (31 per cent.) and constipation was present in 766 (51 per cent.) of this series, making a total of 82 per cent. without any intestinal disturbance. The diet is an important matter and disturbed conditions of the bowels may be due to improper feeding. Much importance has been attached to the gurgling so frequently found in the right iliac fossa, often accompanied with slight tenderness, but it is doubtful if this is of any moment.

The stools should be examined as a routine. In many patients the gross character shows nothing characteristic. If the bowels are loose we usually see what is regarded as the typical typhoid or "pea-soup" stools. These are peculiar in appearance, thin, of a brownish color and may have a curious, almost characteristic odor. Microscopic examination may show portions of sloughs and red blood cells. *Occult blood* is not uncommon, usually in the third or fourth week. It may be found some days before a hemorrhage and at times well into convalescence. Occasionally green stools are passed, the color being due to biliverdin.

Diarrhœa.—This was present during the course in 260 patients (17.4 per cent.) and in less than one-third of these was it severe. The number of stools with diarrhœa is usually from 4 to 6 *per diem*, though as many as 10 or even more may be passed but this frequency rarely lasts long. The diarrhœa which is so frequent at onset—34.4 per cent.—is usually explained as being due to simple intestinal catarrh but the action of purgatives and the influence of diet must be added. Impure milk may be the cause and broths or beef tea may cause diarrhœa. During the course of the disease it may be due to ulceration. Instances of severe persistent diarrhœa are sometimes associated with extensive ulceration

in the colon. In some cases the stools have a dysenteric character, usually associated with severe lesions in the colon which may be diphtheroid.

Constipation.—This was the rule in 766 of the series (51 per cent.) and seems to be a favorable condition for the patient. If the bowels are not moved frequently enough by enema, fecal impaction may occasionally occur but this can be prevented by care. Abdominal pain during the course and slight elevations of temperature in convalescence may be caused by constipation.

Meteorism.—The descriptions of the older writers suggest a frequency much greater than we have today. Not frequent early in the disease as a rule it is most common at the height of the attack when it is of considerable gravity because it indicates severe toxemia and probably increases the dangers of other intestinal complications. By its mechanical pressure on the diaphragm it may seriously interfere with respiration and the action of the heart. The distension is usually greatest in the colon but the small intestine and the stomach may be involved. The influence of opium in favoring meteorism must not be forgotten, and is one of the arguments against its use in typhoid fever.

Abdominal Pain.—This is present in a large number of cases at some period of the attack. With the onset it occurred in 443 or 29.5 per cent. which does not include the cases in which tenderness only was present. A series of 500 cases was specially studied with reference to this symptom with the following results:

1. Without pain or tenderness at any time—206 or 41 per cent. In this group were instances of several of the abdominal complications but none of perforation; 9 cases of hemorrhage and 1 of abscess of the liver were included. As a rule the cases were of a mild type as was shown by the small number of deaths, namely 8.

2. With tenderness but no pain—72 or 14 per cent. These showed no special features, the common position of tenderness being the right iliac fossa.

3. Pain present—222 or 44 per cent. In 61 of these the pain was present only at the onset, which leaves 161 or 32 per cent. with pain during the course. Some patients may be so dull or delirious that no complaint of pain is made but if they are carefully watched some indications can often be observed. The conditions under which pain occurs may be grouped as follows:

(*a*) *Those apart from any lesion of the disease,* such as hysteria, neurotic conditions, hyperesthesia, lung and pleural conditions, pericarditis, hepatic or renal colic, distension of the bladder, cystitis, menstruation, labor, and abortion. Pain in neurotic patients occurs at times without any cause being found. Pneumonia and pleurisy may cause abdominal pain. In the rare cases in women when menstruation is present, there may be pain. The cases in this group are usually readily recognized by a careful examination.

(*b*) *Conditions of the Alimentary Tract Apart from Complications.*—These include improper feeding, vomiting, colic, diarrhœa, and constipation. Severe pain may follow the taking of solid food during the course. Pain with vomiting always suggests some complication. When

it occurs with diarrhœa it may be like that of colic and not continuous, being felt just before the stool or while the bowels are moving. Pain may be caused by fecal impaction which is a cause more often toward the end of the attack. An enema or an irrigation may cause pain. The recognition of the cause is usually not difficult in this group.

(*c*) *Abdominal Conditions Apart from the Specific Bowel Lesions.*—Among these are appendicitis, peritonitis (other than that due to perforation), cholecystitis, intussusception, intestinal obstruction, meteorism, liver abscess, suppurating mesenteric glands, painful spleen and phlebitis, especially of the iliac veins. Pain due to the first three requires no discussion. Obstruction of the bowels is rare in typhoid fever. Pain in the region of the spleen is not uncommon. The pain of iliac phlebitis may be very severe and not yield readily to ordinary treatment. In one patient of this series the abdomen was opened for this cause. The recognition of the cases in this group may be most difficult and in some an exploration is the only certain method. Fortunately for many of these doubtful cases laparotomy is essential for treatment.

(*d*) *Hemorrhage and Perforation.*—These are discussed elsewhere.

(*e*) *Without any Cause being Found.*—This is a large and important group, including 70 of the 161 cases with pain. In certain of these the pain was severe but as a rule not prolonged. Some are of special interest, in that with marked abdominal features there was a leukocytosis varying from 10,000 to 17,000. Exploration in one showed no cause, in another signs of an early peritonitis were found. In 2 no cause could be found at autopsy. The explanation in the majority of this group is difficult to give. A local peritonitis must be rare and at the most could only account for a small number. Deep ulceration is not a frequent cause of pain. The inflamed serosa over an ulcer may cause pain, but this is not usual judging from experience with patients operated on under cocaine, who as a rule do not make any complaint of pain when the peritoneum over an ulcer is touched. Whether enlarged mesenteric glands are a cause of pain is hard to decide. Patients operated on under cocaine have not made any complaint when the glands were touched.

No explanation can be given in many of the cases. In the inflammatory conditions, distended bladder, etc., the reason is evident. But why there should be pain with hemorrhage or distension is not clear. Lymphangitis has been suggested as an explanation in some instances. Abdominal pain should always be regarded as a danger signal, demanding careful examination. The "extra-abdominal" conditions are usually easily ruled out, the others may give great difficulty. The patient should be studied with perforation in view—it is well to be prepared to recognize the most serious possibility. If there are marked features suggestive of a complication and the attendant means to operate himself, everything should be in readiness so that no time may be lost if the need arises. If a surgeon is to be called, he should be given the chance of seeing the patient early so that he may be able to decide not only whether he shall operate or not but *when*. To call the surgeon after general peritonitis has appeared is not fair to the patient or to him.

One other point deserves emphasis—*opium should not be given for abdominal pain in typhoid fever.* Give opium and all chance of early recognition of the most important complication is gone.

Hemorrhage.—As a rule we only consider bleeding from the bowels under this heading, although in rare instances—3 of this series—there may be profuse gastric hemorrhage, apart from that in the hemorrhagic type or from an ordinary gastric ulcer. It is well to make a distinction between the cases in which only a small amount of blood is passed and those in which there is a considerable quantity, as it is by no means rare for patients to pass small amounts of fresh blood with a stool from hemorrhoids or a fissure. Such should not be considered as hemorrhages. Occasionally patients pass small amounts of altered blood or a single small clot, the amount not being more than a few cubic centimeters. If the stools are carefully examined these will be found fairly often but such can hardly be termed cases of hemorrhage. There is always difficulty in comparing the statistics regarding hemorrhage unless it is stated whether or not this group is included. However, these patients should always be watched carefully as severe hemorrhage may follow later.

The average of a large number of cases is about 7 per cent. It occurred in 118 cases of this series (7.8 per cent.). Among a total of 23,271 collected cases there were 1641 of hemorrhage (7 per cent.).

A distinction should be made between the early hemorrhages, which are rarely serious, and the more frequent later ones. The former are probably due to oozing from the hyperemic patches and the amount is usually small. The ordinary hemorrhage during the course is a serious complication. The amount of blood lost may vary from a few cubic centimeters to a liter and there may be one large hemorrhage or repeated ones of varying amount. The patient's general condition may show no change or he may become exsanguine and be in a state of profound shock, with subnormal temperature, profuse sweating, cold extremities and a rapid feeble pulse. There are all variations between these extremes.

The time of most frequent occurrence is toward the end of the second and through the third week. Of the cases in this series in which the time of the first hemorrhage was definitely known, 1 was in the first week, 22 in the second, 38 in the third, 20 in the fourth, 13 in the fifth, 4 in the sixth, and 1 in the seventh week. The latest day was the forty-third. In one patient the temperature had been normal for eleven days before the occurrence of a hemorrhage. In another a hemorrhage of 500 cc. was on the last day of fever in the primary attack, a relapse beginning five days later. They may occur with the temperature almost normal. The greatest interval between the first and last hemorrhage was fourteen days, in a patient who lost small amounts on the eighth and twenty-third days. Another with seven hemorrhages between the twelfth and twenty-fifth days lost 2250 cc. It seems to occur infrequently in a relapse (only in 2 of this series among 173 cases).

The number of hemorrhages varies. Of the cases with definite notes, 1 hemorrhage occurred in 48, 2 in 18, 3 in 11, 4 in 8, 5 in 6, 6, 7, and 10 in 2, 8, 9, and 11 in 1 each. In 6 the bleeding was more or less continuous and the number could not be estimated. The passage of blood from

the bowel is the only positive proof we have of hemorrhage but this does not necessarily give a correct idea of the bleeding, for after repeated small hemorrhages only one bloody stool is passed, or part of the blood from one hemorrhage is passed fairly fresh and the remainder much altered several days later. The largest total amount passed by any of the patients was 2550 cc. in five hemorrhages during a period of fourteen days. Another lost 2000 cc. in three hemorrhages. Twelve lost over a liter of blood.

As regards any exciting cause for hemorrhage we can say little. It may be the first symptom in an ambulatory case. With careful feeding the diet does not seem likely to be a cause, although it is possible that the taking of solid food too early might have some influence. There is no proof that hemorrhage occurs more frequently under the bath treatment. Sometimes blood may come with an irrigation or enema, as happened in 12 patients (not including those in whom the enema was given some days after a hemorrhage and brought away altered blood) but in none was the quantity over 100 cc. There is usually no warning of hemorrhage beforehand. At times it is suggested by the patient suddenly becoming very restless, an altered appearance or sweating. Sometimes the pulse shows a marked change, not so much in the rate although this may be increased, as in a curious bounding quality, which may make one almost sure that hemorrhage has occurred, hours before any blood is passed from the bowel.

The symptoms depend on several factors, the condition of the patient, the amount and rate of the bleeding, and the number of hemorrhages. Thus in a strong, robust individual one moderately large hemorrhage or several small ones may have no effect while in one who is debilitated a moderate loss may make a profound change. However, even a moderate hemorrhage usually has some effect on any patient. In an average case there is pallor, the surface and extremities are cold and sweating may be present. Vomiting, sometimes of blood, may occur. The patient may complain of weakness. The temperature usually falls, and the drop may be as much as 10° and to below normal. Still even a sharp hemorrhage may have no effect on the temperature. The pulse-rate rises and with it the quality alters. At first sometimes bounding, later it becomes small and running. The blood pressure falls usually to 80 or 90 mm. Hg. The lowest record in this series was after one sudden hemorrhage of nearly a liter when the blood pressure fell to 55 mm. Hg. The changes in the blood count depend on the previous condition and the amount of blood lost. There is naturally a rapid drop in the hemoglobin and number of red cells. The fall may be marked, thus in one patient after severe bleeding the hemoglobin fell from 82 to 40 per cent. and the red cells from 5,000,000 to 3,300,000. In another anemic patient the hemoglobin fell from 56 to 27 per cent. and the red cells from 3,000,000 to 1,900,000 within a day. The number of leukocytes may not be altered. If an increase occurs this is usually not extreme, the count rarely exceeding 15,000 per cmm. The highest in this series was 27,900 per cmm. The maximum is usually attained within twenty-four hours, and there is generally a return to normal

within a week. In one the leukocytes fell from 11,300 to 3700 in four days.

A point of importance is the coagulation time of the blood in patients who have hemorrhage. The average for 108 patients of this series, none of whom had hemorrhage or jaundice, was 3.5 minutes. Of these only 7 (6.5 per cent.) had a coagulation time longer than five minutes and only 4 of these were over six minutes. In 3 of these the time was reduced to normal by the use of calcium salts. The average coagulation time of 22 patients with hemorrhages was 4.2 minutes. It was over five minutes in 6 (27 per cent.) and 5 of these were over six minutes. In nearly all of these the time was reduced to normal by the use of calcium salts. These figures are too small for positive conclusions but are suggestive. Severe hemorrhage occurred in patients with normal coagulation time but nearly all the patients with very prolonged coagulation time had profuse hemorrhage.

Abdominal pain with hemorrhage is not uncommon and may be severe. In some it has been present for two or three days before but this may have been only a coincidence. After a hemorrhage it is best to avoid any more examination of the abdomen than is necessary and palpation should be very light. The time when the bleeding actually occurred and the passage of blood from the bowel may be hours or days apart, but an idea of the interval can often be obtained by the appearance of the blood. In the large single hemorrhages the stool is usually fluid and reddish in color and in estimating the quantity of blood one must remember how much color a small amount can give to a considerable quantity of liquid. In other instances the stool may consist of fluid and clotted blood. The occurrence of clots is often regarded as indicating profuse sudden bleeding, probably from a large vessel. In repeated hemorrhages the blood may be fresher in each successive movement from the bowels. If the blood remains some time in the bowel it may be much altered and passed as dark clots.

The *results* are very various and there is no doubt that some patients do seem to be benefited. These are usually robust and not very toxic. The temperature may be lower, the pulse not increased or even decreased in rate and the whole character of the attack milder. There are two forms which stand out, the large single hemorrhage with marked effects and the repeated smaller ones. The former is rarely fatal, for the danger comes from repetition and comparatively few die directly from one bleeding. In collecting statistics of the fatality of hemorrhage there is one source of error as if all are included who had hemorrhage followed by death at any interval a false idea of its danger is obtained. Thus a patient may have hemorrhage and die a week later from perforation or after two or three weeks from toxemia and asthenia, the hemorrhage having contributed only to influence the general condition, or a patient who is very toxic may pass a small amount of blood and die soon after, but it is doubtful if the hemorrhage should be considered as the cause of death. The figures given by writers vary widely but the usual statement is that 20 to 30 per cent. of the patients die. Among 118 cases in this series there were 12 deaths, only 10 per cent.

Perforation.—The figures as to its occurrence vary greatly. The Munich series of 2000 autopsies showed perforation in 5.7 per cent., Murchison in 435 autopsies, 13.8 per cent., Curschmann in 575 autopsies, 16 per cent. The figures of Herschel, and Broardel and Thionet among a total of 2667 autopsies showed perforation in 7 per cent. Mackenzie found that 351 out of 1037 deaths from typhoid fever in certain London hospitals were due to perforation. In this series of 105 autopsies, perforation was found in 30 (28.5 per cent.), so that among a total of 6819 autopsies there were 834 cases of perforation (12 per cent.). Of the 137 deaths in this series 33 (24 per cent.) were due to perforation. In recent years many patients are saved who formerly died of toxemia, whereas we have not reduced the mortality from perforation to a corresponding degree. This is well brought out in the series reported by Hare of Brisbane, for among 1828 cases treated by the expectant method, perforation occurred in 2.9 per cent. and was the cause of death in 20 per cent. of the fatal cases. Among 1902 treated by baths the incidence of perforation was the same (2.9 per cent.), but its proportion among the fatal cases rose to nearly 40 per cent.

When we turn to the incidence in clinical reports we find much more agreement and as a rule hospital figures show perforation in from 2 to 3 per cent. of all cases. German statistics for 6321 patients (Curschmann, Hamburg records, Griesinger) showed 117 (1.8 per cent.), Murchison in England found 48 among 1580 (3 per cent.), Mackenzie from London hospitals reports 351 among 9713 (3.6 per cent.), J. McCrae in 717 in Montral in 43 (6 per cent.), Hare of Brisbane in 2.9 per cent. of 3723, the London Fever Hospitals 294 among 8356, and Scott (Philadelphia) in 84 among 3006 cases. In this series there were 40 of perforation (2.6 per cent.). The total of these figures gives a percentage of 3.1 among 34,916 cases.

The incidence of perforation varies greatly from year to year. As to the influence of sex, perforation occurs more frequently in men. In this series, 32 were males and 8 females, but, taking the number of admissions in each sex, we find that perforation occurred in 1 out of 33 males and 1 out of 55 females, which makes the disparity less. In this series the age was as follows: from one to ten, 3; from ten to twenty, 10; from twenty to thirty, 15; from thirty to forty, 6; and from forty to fifty, 6. Over forty years of age perforation is rare, and in that this series is unusual. The oldest patient was forty-nine years. The children were aged eight, nine, and ten years.

The period of greatest incidence is the third week. In this series the distribution was: first week, 0; second, 10; third, 12; fourth, 7; fifth, 5; sixth, 1; seventh, 2; and eighth 1. The latest case was on the fiftieth day. In 2, perforation occurred while the patients were about and the day of disease could not be determined. Instances have been reported as late as the sixteenth week. Perforation may occur after the temperature has become normal and the patient convalescent. This has been brought about in some by the taking of solid food.

The site is most frequently in the ileum. In this series the perforation was in the ileum in 32, the appendix in 3, the sigmoid flexure in 2, the

cecum in 1, and in one both in the descending colon and rectum. Taking the figures of Liebermeister, Mackenzie, Fitz, and this series, the site was in the ileum in 506, colon 56, appendix 32, Meckel's diverticulum 4, jejunum 4, cecum 1, and in one in both the colon and rectum. The number of perforations may vary from 1 to 25 but in the majority there is but one. Of 39 of this series in which this was determined, there was 1 perforation in 28, 2 in 8, and 3 in 3. The opening was within 40 cm. of the ileocecal valve in 27 and the greatest distance from the valve was 150 cm. Of the 3 with perforation in the appendix, 2 had two openings.

In discussing the *symptoms* we should separate those due to perforation from those of the resulting peritonitis. If this be local, as it may be for a few hours after perforation, there is no special change in the general picture, but in the literature until very recently most of the descriptions of the symptoms of perforation were those of the resulting general peritonitis. It should be our aim to make the diagnosis of perforation before general peritonitis has come on. The recognition of perforation can as a rule only be made if there has been careful preparation for it. In a hospital the house officers should always be alert and ready to attend whenever there are any suspicious symptoms. The nurses or the members of the family, if the patient is being nursed at home, should be told to report any suspicious symptoms immediately. Of these the most important for diagnosis are sudden abdominal pain, nausea and vomiting, any sudden change in the patient's general condition, especially sweating, or any signs of collapse. The report of any of these should always lead to the careful examination of the patient, with perforation in mind. The most important of these is the onset of sudden sharp abdominal pain.

May we have any premonitory symptoms? In some instances the symptoms suggest slight local peritonitis before perforation but this is difficult of proof. Some patients have abdominal pain for days before perforation occurs but when we remember the frequency of abdominal pain and how often it occurs without there being any peritonitis, to interpret such pain before perforation as due to a local peritonitis hardly seems justifiable. Perforation is apparently more likely to occur in patients with diarrhœa. The association of hemorrhage and perforation is not uncommon, as in 10 of the 40 of this series; in 7 they occurred together and in 3 the hemorrhage occurred a few days before. The character of the attack has no marked influence; although in more than half this is severe yet perforation may occur in a mild attack.

The onset may be sudden or gradual, a useful classification emphasized by Manges. The diagnosis in the former group can be made much more readily than in the latter, for the mode of onset is one of the greatest aids. In the latter group the symptoms subsequent to perforation are those on which we must depend, but the outlook, even with early diagnosis and operation, is grave in the group with such severe toxemia that there are few symptoms at onset. In the description of symptoms those given of the onset apply especially to the "acute group." The chances for early recognition are greater when the patient is being given the

bath treatment, as the mental condition is clearer and the onset more readily observed.

Onset.—The first symptom in the great majority is the occurrence of sudden, sharp, severe abdominal pain. This was the case in 26 of 32 patients of this series in whom the onset was noted. Of the others, in 6 there was no note, in 2 the time of onset was doubtful, in 2 the patient was delirious and there was no complaint of pain, in 2 the patient was admitted with general peritonitis and gave no history, in 2 the perforation occurred just before death from toxemia. In some patients dying from toxemia, perforation may occur while the patient is moribund. In these there may be no symptoms and a diagnosis is impossible; operation is out of the question, and the condition can be recognized only at autopsy.

The mode of onset is the most important point in the recognition. If the patient is seen then it may be possible to make a diagnosis with reasonable certainty, which later on can be made only with great difficulty. The pain is usually paroxysmal and rarely constant. Between the attacks the patient may be fairly comfortable and show no definite signs, so that it is important to sit down by the bedside and watch for some time. As a rule the pain returns before a long interval but may last only for a short time. The seat of the pain of onset varies considerably but is usually in the lower abdomen, sometimes about the navel or in the right iliac fossa. In males it may be referred to the penis. With the pain the patient may complain of bladder irritability with frequent micturition. On examination one may find no special change in the abdomen. The respiratory movements may be slightly diminished but this is not common. On palpation there is usually marked tenderness, sometimes over the whole abdomen, sometimes localized. There may be some rigidity and possibly muscle spasm, but as a rule shortly after perforation these are not persistent and may be present only during the attacks of pain. With the local abdominal features there may be general disturbance, such as a marked change in expression, sometimes associated with sweating or a chill. In some instances there is nausea or vomiting. These are all usually temporary if they appear at the time of perforation. There may be an increase in the respiration and pulse-rate. The fall in temperature, so often described, is not constant. There is more often slight elevation for two or three hours following the perforation and then a fall.

With suspicious signs, careful notes should be made at once of the general symptoms and the local conditions. Of these the most important are the degree of distension, the extent of the respiratory movements, the amount of tenderness, and the presence of rigidity or of muscle spasm. With this there should be hourly records of the temperature, pulse, and respiration, with the blood pressure taken every fifteen minutes. All this represents much work, but it must be recognized that if we are to make an early diagnosis of perforation we must be prepared to devote every energy toward it.

In the few hours after perforation there may be little change. The pain may recur at intervals, generally paroxysmal in character, but

otherwise there is little alteration. The principal features can perhaps best be discussed separately.

1. *General Appearance.*—This may be suggestive at the onset, the features having a more or less pinched expression especially if there be sweating. As a rule this does not persist and in a few hours later there may be nothing marked. If general peritonitis develops we have the characteristic facies of that condition.

2. *Temperature.*—The course of this is variable. In many patients immediately following perforation there is a slight elevation followed later by a drop. There is no rule and a sudden fall or sudden elevation may occur. Later the temperature may rise with the peritonitis, but changes in the temperature are too uncertain to be of much value.

3. *Pulse and Respiration.*—Usually these both show increase, but there is no certainty in this, for patients have been operated on in whom neither the pulse nor the respiration rates had especially altered. Generally the respiration rate increases at the time of perforation. Later both the pulse and respiration rate increase.

4. *Gastric Symptoms.*—Hiccough, nausea, or vomiting may occur at the time of perforation. These are always suggestive signs and may draw attention to the complication. In several patients, the sudden occurrence of one of these first aroused suspicions of perforation. They are especially important because so rare in typhoid fever.

5. *Abdominal Conditions.*—These are the most important because while other things may arouse suspicions, it is by the abdominal signs that the diagnosis is usually made. Abdominal pain may be fairly constant but is usually paroxysmal. The local abdominal features are: (*a*) Increase in distension, which is often not present until some hours after perforation. It should always be carefully looked for, as increasing distension is a most important point. (*b*) Changes in the respiratory movement: These if present early are very valuable. The decrease in the extent of movement may be seen only below the navel or may be more on one side than the other. But general peritonitis may be present with well-marked retention of the respiratory movement. (*c*) Rigidity: This is a most important condition and should always be most carefully noted. Light palpation should be employed and it is especially important to compare the two sides of the abdomen. With perforation it may be some hours before rigidity is marked and too much importance should not be attached to its absence. Persistent rigidity of one rectus muscle is an important sign. (*d*) Muscle spasm: This is as a rule the most important local sign. It may be quite local and found in part of one rectus only. (*e*) Movable dulness: This may suggest the presence of free fluid in the peritoneal cavity but great caution should be observed in drawing such a conclusion, as it may be given by fluid in the bowel. This is especially likely to occur if there has been diarrhœa, which is often the case in the patients with perforation. (*f*) Obliteration of liver dulness: This is of value, first, if it occurs in an abdomen which is flat or scaphoid, and second, if it has appeared suddenly in a non-distended abdomen. If there be any degree of distension no dependence should be placed on it. (*g*) Signs on auscultation: These are of very

doubtful help. Some writers have laid stress on the fact that gas could be heard escaping from the bowel through the perforation. The writer heard it in one patient with perforation in whom there was also a curious sound on auscultatory percussion comparable to the coin sound in pneumothorax.

6. *Rectal Examination.*—This should always be made, for if the process is low in the abdomen there may be marked tenderness on pressure high up in the rectum, sometimes more on one side than the other.

7. *Bowels.*—As a rule they do not move after perforation but this is not invariable and both flatus and feces may be passed.

8. *Leukocytes.*—Perforation is usually followed by an increase in their number. There are three fairly well-marked groups of cases: the first in which there is a steady increase in the number from hour to hour; the second in which there is a slight increase in the first two or three hours and then a rapid fall, and the third in which there is practically no change or even a fall. The initial rise may be very temporary and disappear in three hours. It is evident that counts can be of service only if there are previous ones available for comparison. Many of the conditions which cause abdominal pain may also produce leukocytosis. It is in the group in which the leukocytes increase steadily that the blood counts give the most assistance. The presence of leukocytosis is most important but from its absence no conclusion should be drawn. A steadily dropping count may suggest a severe general peritonitis.

9. *Blood Pressure.*—In many patients there is a sharp rise with the perforation. This is not invariable, as in some cases the blood pressure does not show any change. Probably any condition causing pain may produce a rise in the blood pressure. It should be of aid in the diagnosis of hemorrhage from perforation.

Advance in the signs is an important aid and the patient should be carefully watched for this. The distension may gradually increase, the respiratory movements decrease and the tenderness with rigidity and muscle spasm become more marked. But one should not wait for too much advance before deciding on exploration.

Lastly, as an aid in the diagnosis of perforation we must include an exploratory incision, for it may be impossible to make a positive diagnosis without this. The important matter to decide is whether there exists an abdominal condition which justifies exploration rather than to make a positive diagnosis of perforation. An acute abdominal complication is what we have to recognize—this is perforation in the majority. In some patients, especially those who are toxic or delirious, it may be quite impossible to make an early positive diagnosis. No one can lay down rules which will always apply—every patient is a new problem. The conditions which are most likely to be mistaken for perforation are as follows: (1) Peritonitis from other causes: This is not common and its definite recognition is difficult. In these cases an exact diagnosis is not an important matter because the treatment is the same as for perforation. (2) Appendicitis: This may be due to a typhoid process or may be distinct and either acute or an exacerbation of a chronic condition. The condition can hardly be positively recognized and the

same remarks apply as to the preceding group. (3) Hemorrhage: This may give a picture much like perforation but the fall in blood pressure and in the percentage of hemoglobin is an aid in diagnosis. The association of the conditions has to be kept in mind and every patient with hemorrhage should be carefully examined with the possibility of perforation in view. Rigidity and muscle spasm are not as common in hemorrhage as in perforation. The difficulty of diagnosis when the two conditions are present is very great. (4) Phlebitis: This in the iliac veins may give very suspicious symptoms and in one such case of this series exploration was done. The careful examination of the leg for swelling and the femoral region for tenderness may give the correct diagnosis. (5) Intestinal conditions, such as obstruction, strangulation, intussusception, may cause difficulty. (6) Attacks of abdominal pain without evident cause. In these patients careful continued examination is the greatest help. The abdominal signs do not usually show the advance which we often find in the perforation cases. (7) All the conditions which have been noted as causing abdominal pain may give difficulty but a careful routine examination should exclude them.

The possibility of recovery without operation, after perforation of the bowel, is an interesting question but it is doubtful if, practically, it is worthy of much consideration. The omentum or adhesions may very rarely close the opening. Certainly it should never be used as an argument against operation. A diagnosis of perforation made without operation or autopsy is open to great doubt. Some patients with suspicious symptoms are operated on and no perforation found, while others may show symptoms which are very suggestive, but dying later of other conditions the peritoneum is found perfectly clear at autopsy. In rare instances a local abscess may follow perforation. This may be drained or rupture internally exactly as an appendix abscess.

General Peritonitis.—The characteristic general expression, the pulse small and running, the temperature variable, sometimes being high but in others low, require no comment. There may be hiccough with nausea and vomiting and but little complaint of pain. The abdomen is usually distended, although there may be general peritonitis with a scaphoid abdomen; the respiratory movements are diminished or absent; there is usually tenderness with marked rigidity and perhaps muscle spasm. The symptoms of perforation are quite distinct in the majority of instances from those of the resulting general peritonitis.

Peritonitis from Other Causes than Perforation.—The frequency of this is difficult to estimate. Some writers put it as high as 1 per cent. or even more. The subject has been carefully studied by Yates.[1] In this series there were four instances, one from a simple appendicitis, one from old pelvic disease, one from ulcer in the gall-bladder without rupture, and one without discoverable cause. The principal causes are as follows: (*a*) Extension from the ulcers. It is difficult to say how often this occurs but it is probably not common. In the same way a local peritonitis may arise from extension from an ulcer in the gall-

[1] *American Medicine*, 1903, v, 700.

bladder. (*b*) From suppurative processes. The possible sources are various, and include rupture of a suppurating mesenteric gland, rupture of an abscess or infarct of the spleen, abscess of the liver, abscess of the abdominal wall, abscess about the bladder, and thrombosis. (*c*) From pelvic conditions. An ovarian abscess, disease in the tube or an infective process in the uterus may be the source. (*d*) Other intestinal conditions, such as appendicitis apart from a typhoid lesion or strangulated hernia. (*e*) Without any evident cause. It is possible that this may be from the passage of bacteria through the intestine or from a periadenitis.

The reported cases studied by Yates showed the time of greatest incidence about the end of the third week. It occurred both in severe and mild attacks and with slight and deep ulceration. In the majority the onset was acute and as a rule the diagnosis of a perforation was made. Abdominal pain was the most constant symptom and was usually on the right side. Rigidity was usually found at some time. The temperature curve was variable. Of 11 patients operated on, 4 recovered; and of 9 not operated on, all died. The type of peritonitis varied from serofibrinous to fibrinopurulent.

Ascites.—This has occurred in rare cases (McPhedran).

Conditions of the Rectum.—Ulceration occurs in a moderate number of cases and there is danger of perforating the ulcers in the giving of irrigations or enemata, usually with the production of an abscess.

The Spleen.—While enlargement of the spleen is common in infectious diseases generally, yet in none has it the same importance as in typhoid fever. The recognition of splenic enlargement is most certain by palpation. Percussion is of value in determining increase in size, especially when the spleen cannot be felt, but distension of the colon and stomach may interfere with this. There are certain conditions which prevent the spleen being palpated even when it is much enlarged; thus if the thorax be very deep, only an enormously enlarged spleen can extend to the costal margin. In patients who have very thick abdominal walls the spleen may not be felt. It is doubtful whether previous conditions, such as adhesions, affect the enlargement materially.

Enlargement as a rule is greatest at the height of the attack, although the spleen may be palpable very early. In some patients it may first be felt when marked emaciation has rendered palpation easier. There may be a marked reduction in size after intestinal hemorrhage. As a rule the spleen diminishes in size in the latter part of the attack, although in some patients the enlargement may continue after the temperature is normal. It is safe to consider these as in greater danger of a relapse. If the spleen has become much reduced in size after the original attack, the enlargement may return with a relapse but rarely with a recrudescence. In some instances the spleen is felt for the first time in the relapse. The spleen was felt in 1075 of the 1500 cases (71.6 per cent.).

The spleen is usually soft, although in patients who have had malarial fever it may be quite hard. As a rule it is not tender, although some patients complain on palpation. In some there is complaint of pain in the left costal region which may be persistent and not made markedly

worse by palpation. The occurrence of perisplenitis may be suspected and this diagnosis may be made if the pain be severe and rendered more so by deep breathing, pleurisy being excluded. Other conditions such as spontaneous rupture, infarct, abscess, etc., are rare but are sometimes possible of diagnosis.

Liver.—This organ plays little part in an ordinary attack and subjective symptoms referred to it are rare. There may be complaint of pain in the liver region with tenderness and perhaps slight enlargement. The common focal necroses in the liver do not give any clinical symptoms so far as we know, although in some they may be associated with jaundice. The most important liver conditions which occur are jaundice, abscess, suppurative pylephlebitis, and cholangitis.

1. *Jaundice.*—This may occur as catarrhal jaundice, toxic jaundice, or with abscess and cholecystitis. It is rare and, apart from abscesses and cholecystitis, was present in 8 patients in this series. The coexistence of gallstones may be a cause. (*a*) Catarrhal jaundice: This is usually of a mild grade and seldom causes any severe symptoms. It is rare at the beginning but may occur at the height of the attack or in the latter part of the course. It may be quite possible to distinguish between a catarrhal and a toxic jaundice. The occurrence in milder attacks and the absence of bile in the stools are in favor of the catarrhal form. (*b*) Toxic jaundice: This is more likely to occur in severe attacks and late in the course. Bile is usually present in the stools. In some instances a condition much like acute yellow atrophy has been described, with a rapid course with jaundice, marked decrease in the size of the liver, hemorrhages, and a termination in coma.

2. *Abscess.*—This is rare and was present in only two of this series during the attack, while in a third patient an amœbic abscess developed during convalescence. The abscess may be single or multiple, the latter usually occurring as part of a general septic process and perhaps associated with parotitis, perichondritis, etc. In others it may be secondary to infection in the abdomen, such as mesenteric abscess or pylephlebitis. Multiple abscesses have occurred after cholecystitis. The causal organism is the typhoid bacillis, the colon bacillus, or pyogenic cocci.

The symptoms are pain in the region of the liver, increase in its size, marked leukocytosis, and possibly the muddy color of the skin sometimes associated with abscess. Pus may be obtained by exploratory puncture. The conditions from which abscess has to be diagnosed are cholecystitis, subphrenic abscess, and empyema. A liver abscess in typhoid fever may be latent and discovered only at autopsy. Von Eberts[1] recently collected 30 cases and studied the findings. The most characteristic features in his series were pain in the upper right quadrant of the abdomen, fever of a septic type and enlargement of the liver, or the presence of a mass. Jaundice was generally absent.

3. *Suppurative Pylephlebitis.*—This is very rare and is usually associated with thrombosis of the portal veins. Osler has reported a case associated with mesenteric abscess.

[1] *American Journal of the Medical Sciences*, 1911, cxli, 803.

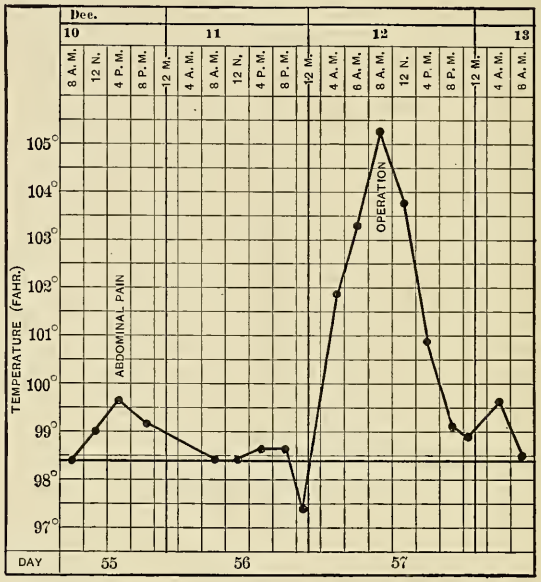
Gall-bladder.—The relations of typhoid bacilli to the gall-bladder are as follows: (*a*) In the great majority, perhaps always, typhoid bacilli are present in the gall-bladder during the attack. (*b*) The bacilli may persist in the gall-bladder for an indefinite period. (*c*) Typhoid bacilli may occur in the gall-bladder as a local infection without the patient even having had typhoid fever.

During an attack the typhoid bacilli probably reach the gall-bladder through the blood. They may be excreted from the liver or gain access through the ducts but this latter method does not seem probable. In the majority no symptoms are set up, and in cholecystitis it may be difficult to assign any reason for the complication beyond the presence of the bacilli. In a certain number, the determining factor is the presence of gallstones but this is not common during the attack, being found only in 4 out of 115 cases collected by Camac, although the formation of gallstones may be very rapid. The organisms may be found in clumps in the gall-gladder. Secondary infection with other organisms is rare. Obstruction to the flow of bile undoubtedly favors cholecystitis which in some grade is probably much more common than is usually supposed, as only the more severe attacks are noted. The diagnosis was made in 19 of this series (1.2 per cent.). The extent of the process may be very variable. There are probably all stages from a simple catarrhal cholecystitis to ulceration and perforation. In rare cases there may be extension and a local peritonitis without any perforation of the gall-bladder. The time of the occurrence of cholecystitis varies greatly, the earliest in this series being on the eighth day and the latest on the fiftieth day. It may appear at the height of the attack or after the temperature is normal and it may be difficult to say whether it should be regarded as a complication or a sequel. The majority occur during the third week or later, sometimes with a relapse.

The onset is usually sudden with pain in the region of the gall-bladder. There may be a chill or vomiting. The pain usually persists and may be situated close to the costal margin or lower down on the right side. On palpation there is usually marked tenderness over the right side of the abdomen, especially in the upper quadrant and with this rigidity and muscle spasm. In the febrile cases there may be an increase in the temperature or a sudden rise if the temperature has become normal as shown in Figs. 7 and 8. The pulse-rate usually increases and in some the respiration also. There may be diminished respiratory movement both of the thorax and abdomen on the right side. Vomiting or a chill may occur after the onset. Jaundice may follow and was present in 6 among 19 cases. There is usually leukocytosis, generally from 10,000 to 15,000, rarely reaching 20,000. The gall-bladder is sometimes felt. The progress of the condition is very variable. It may persist for a few days, usually four to eight, and then disappear or go on to perforation. The symptoms of perforation require no special discussion but it has to be remembered that when a patient has been having abdominal pain from cholecystitis for some days there may not be change enough to suggest a perforation before the onset of general peritonitis. Perforation may happen in a gall-bladder which is not palpable and not especially

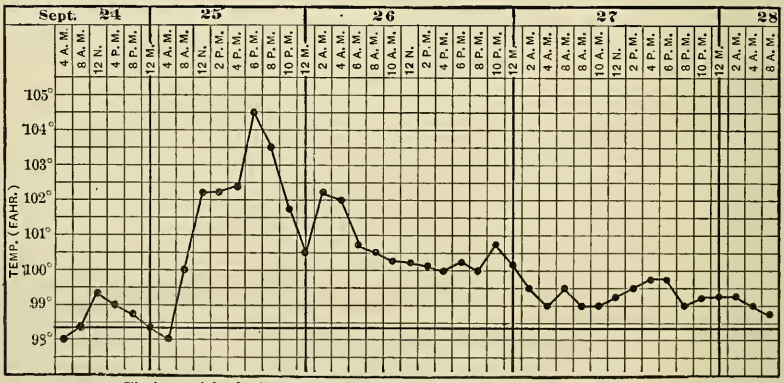
enlarged. General peritonitis usually follows perforation; there are rare instances of the process being localized. In very toxic patients, perforation and general peritonitis may be present before the condition is recognized. The patient should be watched most carefully and frequent records made just as in the case of suspected intestinal perforation. Tapping the gall-bladder is not justifiable.

FIG. 7



Cholecystitis during convalescence. Operation. Recovery.

FIG 8



Cholecystitis during convalescence. Recovery without operation.

Pancreas.—Hemorrhagic pancreatitis is very rare but has occurred.

RESPIRATORY SYSTEM.—*The Nose.*—Early in the disease there may be hyperemia of the nasal mucous membrane, although coryza is rare.

This may result in the passage of a little bloody mucus but frequently there is definite bleeding. Epistaxis occurs frequently during the incubation and also in the early febrile stage. It may occur during the course or even in convalescence. It is much more common at the beginning of typhoid fever than any other acute infection and occurred at onset in 323 of this series (21.5 per cent.). As a rule, the bleeding is rarely profuse, but it may prove alarming and a few cases are on record (apart from the hemorrhagic type) in which death resulted directly from the epistaxis. In the hemorrhagic type it may be very severe.

The Larynx.—Serious involvement is recognized in a comparatively small number of cases. In patients who are very ill and breathe through the mouth, both the pharynx and larynx show a condition which may be termed a "dry catarrh." A simple catarrhal inflammation may be present but ulceration of the mucous membrane is more serious. This was found in 3 cases of this series at autopsy, in one associated with necrosis of cartilage. Jackson has divided the lesions into: (1) Subacute laryngitis, (2) ulcerative laryngitis, and (3) perichondritis. The first was found in 237, the second in 68, and the third in 17, of 360 cases. Ulceration occurred usually after the third week, the average being the thirty-first day, and in patients with severe infection. Two-thirds of his patients recovered perfectly. The process may be primary in the cartilage. One patient of this series coughed up both arytenoid cartilages. In some instances the changes in the larynx have resulted in stenosis. Œdema of the glottis occurs, as was found in 2 of this series at autopsy; ulceration of the epiglottis was found in 1.

The laryngeal complications are often overlooked, as in patients who are very toxic no complaint is made and examination of the larynx is often difficult. There may be dyspnœa, hoarseness, and cough, or even loss of voice. The patient may complain of pain and probably have difficulty in swallowing with pain on pressure over the larynx. The danger of acute œdema of the glottis makes it necessary to watch these patients carefully. Paralysis of the laryngeal muscles occurs rarely and is probably due to neuritis.

Respiration.—The rate is often increased, perhaps to 24 or 28 per minute, even when no complication is present. Dyspnœa is rare.

Bronchitis.—This is one of the early symptoms, although the patients rarely make any special complaint of it. Usually regarded as almost a specific symptom, the bronchitis shows no special peculiarities. The cough is frequently harsh, with scanty and rather tenacious sputum, occasionally containing small amounts of blood. The principal physical sign is the presence of numerous rales. In some instances the cough is unusually severe and slight cyanosis is present. The severity does not necessarily bear any relation to the character of the attack, as mild infections may show severe bronchitis. As a rule it lessens in the second week and often disappears very rapidly but in some patients it proves troublesome throughout or returns during the latter part of the attack. Occasionally collapse of the lung or bronchopneumonia follows. The occurrence of typhoid bacilli in the sputum is a point to which attention should be given. Bronchitis does not appear to be of importance in the

fatal cases and was noted in 4 of 105 autopsies, in 2 of which it was described as putrid bronchitis.

Lobar Pneumonia. The figures in the literature as to its frequency are variable, some considering that it occurs in 10 per cent. of all cases. This does not agree with this series, as lobar pneumonia was found in only 22 cases (1.5 per cent.). It occurred in 233 of 8356 cases in the London Fever Hospitals (2.7 per cent.). It is convenient to separate two conditions under which it occurs. (1) At onset: This is termed pneumotyphoid by French and German writers and occurred in 3 of this series. The attack begins with the usual features of lobar pneumonia, chill, pain in the side, fever, and characteristic signs in the lung. The attack may run the course of an ordinary lobar pneumonia without a suspicion of anything else being entertained and only the persistence of the fever suggests another condition. There may be a termination by crisis, the temperature falling to normal for a day and then rising again. It may be difficult to say whether we have an ordinary lobar pneumonia followed by typhoid fever or typhoid fever with early involvement of the lung. In one patient with no intestinal lesions there was consolidation of one lung, associated with gangrene, the organism present being the typhoid bacillus. (2) It may occur during the course, as in 19 of this series, and is most frequent during the second and third week. The symptoms may be few in number, the patient not making any complaint of pain or distress, especially if the mental condition be dull, and only an increase in the respiration rate with cyanosis may draw attention to the condition. Leukocytosis may not be present. The sputum may be slight in amount or swallowed but in some instances has the characteristic rusty appearance. Lobar pneumonia was found at autopsy in only 6, a rather small percentage.

Bronchopneumonia.—This is usually a terminal event. In 8356 cases from the London Fever Hospitals it was found in 1.2 per cent. It was found at autopsy in 37 of this series (35 per cent.). In some it is due to the typhoid bacillus but in the majority to pyogenic organisms. Coming on as a rule when the patients are very ill it may not give rise to any marked symptoms. The onset may be with a chill. The increase in the respiration rate, cyanosis, and physical signs give the diagnosis. Œdema, abscess, or infarction may be associated. In some cases there may be an aspiration pneumonia, especially in patients who are very dull. In patients with ulceration in the larynx there is always great danger of secondary pneumonia.

Infarction.—The occurrence of atypical conditions in the lungs and pleura is not uncommon. The signs may be indefinite and suggest pneumonia or pleurisy. It is probable that these are due in many cases to small infarcts from areas of thrombophlebitis. Conner[1] has drawn attention to this point and makes three groups: (1) In which a friction rub or crepitant rales were heard over a small area for a few days. (2) Cases with the signs of a small patch of consolidation, usually in a lower lobe and lasting only a few days. (3) Cases with extensive pleurisy

[1] *Transactions of the Association of American Physicians*, 1912, xxvii, 198.

or pleural effusion. Infarction of the lung was found in 4 cases of this series at autopsy.

Hypostatic Congestion and Pneumonia.—These are especially likely to occur in patients with long, severe attacks. If they appear early it is of serious import, although as a rule their occurrence is late and favored by cardiac weakness and the position of the body. This latter is important and the endeavor should be made in all severe attacks to keep the patient turned on one side or the other and off the back as much as possible. But by far the most important preventive of hypostatic pneumonia is the bath treatment. It was found in only 2 of this series at autopsy. It may not give rise to any symptoms and will rarely be recognized unless a routine examination is made. As a rule there is defective resonance at the base, the note having a slight tympanitic quality. The vocal fremitus is often difficult to obtain. It may be diminished if the bronchi are full of mucus or the voice very feeble, but otherwise is somewhat increased. The breath sounds are usually feeble and as a rule there are numerous moist rales. Such a condition may be associated with bronchopneumonia or œdema. Hypostatic pneumonia is an exceedingly dangerous condition and, if well established, recovery rarely occurs.

There are other lung complications which occur occasionally. Abscess is infrequent and may be associated with pneumonia or general septic infection. It was found in 4 of this series at autopsy in association with bronchopneumonia. Gangrene is also rare and as a rule occurs late in the attack. It was found at autopsy in 2 cases, in one with thrombosis.

Hemoptysis.—This may occur in the hemorrhagic type. In a few patients small amounts of blood are brought up, most of these being due to an intense bronchitis. It may be due to an associated pulmonary tuberculosis. Some are probably due to small hemorrhagic infarctions.

Pleurisy.—This is not very common, having been noted in 32 of this series (2.1 per cent.). It was found at autopsy in 9 cases. Pleurisy may be common in some epidemics. It was present in 92 of 8356 cases in the London Fever Hospitals (1.1 per cent.). Pleurisy may occur at the onset or more frequently during the course. The onset may be sudden with high fever, severe pain in the side, and a well-marked friction rub. The majority in this series were of the fibrinous type and in only 4 was there effusion. This may be serous or purulent, there having been three of the former in this series and one of the latter from which typhoid bacilli were obtained. The purulent type is most often seen during convalescence. In many instances pleurisy is secondary to conditions in the lung, such as pneumonia, infarct, and gangrene. Hemorrhagic effusions have been noted and there is the possibility that a tuberculous pleurisy may coexist with typhoid fever.

The question of the organism concerned in the lesions of the respiratory tract is an interesting one. The ulcerative processes about the larynx are due in the majority to the pyogenic cocci but in a small number typhoid bacilli have been obtained. In the lung the determination of the causal organism may be difficult. The typhoid bacillus is probably present in the lungs in every case and can frequently be obtained

by puncture. However, the examples of lobar pneumonia due to the typhoid bacillus alone are few. In the majority the pneumococcus is present, and may be associated with the typhoid bacillus. That the typhoid bacillus alone may be responsible is supported by the fact that in one case of lobar pneumonia a paratyphoid organism was obtained in pure culture. It seems fair to hold that while in the majority of cases lobar pneumonia is due to the pneumococcus, with which the typhoid bacillus is often associated, yet in rare cases the typhoid or paratyphoid bacillus is the causal organism. In bronchopneumonia, the typhoid bacillus is probably present more frequently than in lobar pneumonia. Among 14 cases with satisfactory cultures, the typhoid bacillus was obtained in pure cultures in 2, both the colon and typhoid bacillus in 2, colon and typhoid bacillus with staphylococcus in 1, pneumococcus in 1, pneumococcus and colon bacillus in 2, pneumococcus, colon bacillus and staphylococcus in 2, streptococcus in 2, and staphylococcus and bacillus proteus in 1 each. In gangrene and abscess the typhoid bacillus may be obtained in pure culture.

The Circulatory System.—The conditions in the patients of this series have been especially studied by Thayer. As a rule the state of the circulation is an important indication of the condition. A variable degree of capillary stasis is common and may be extreme, especially over the back, but does not seem to be of any special moment. The pulse may not give any characteristic findings. As a rule during the early stages, the increase in the rate is less than would be expected from the fever. This may be true of some patients all through the attack, the rate never reaching 100. Thus, among the last 500 cases in the series there were 176 in which the pulse-rate was not above 100, in 60 not over 90, and in 21 the rate was not over 80.

Dicrotism.—There is no disease in which a dicrotic pulse occurs so frequently. It may be marked early in the course and continue throughout. In rare cases the pulse may show several secondary waves. The dicrotic pulse is most marked in adults, but in patients with arteriosclerosis it may be absent.

Rate.—At the height of the disease the pulse may show marked variation. It may become very rapid, 140 or over, and then it is usually small and running. These patients as a rule are seriously ill and the prognosis is always grave. The pulse-rate may show a marked response to any nervous influence but a sudden increase should always suggest careful search for a possible complication. With the onset of pneumonia the rate may rise but it is especially important with abdominal complications, notably hemorrhage and peritonitis. Hemorrhage of any amount usually causes marked increase and this may suggest bleeding before any blood is passed. With perforation and peritonitis there is some increase in the majority of cases. In very severe attacks toward the end the pulse may become so rapid and running that it can hardly be counted. The records of this series show that in 223, or 15 per cent., the pulse rate rose above 140. Of these, 46 were under fifteen years of age, and of the remaining 177 patients 86, or 48.5 per cent., died. In 77 patients the pulse-rate rose above 150 and 55 of these,

or 71.4 per cent., died. In 51 patients the rate rose above 160 and of these 35, or 68.5 per cent., died. In 6 the rate rose above 170 and of these 4 died. In 2 a rate of over 180 was noted and 1 of these died. Death followed in both instances in which the pulse could not be counted. Irregularity is not common but if present with a rapid rate is of serious import, and of 13 patients with a pulse-rate above 140, associated with irregularity, 9 died.

The baths make a considerable change in the quality of the pulse. While in the tub the pulse usually becomes small and there may be difficulty in feeling it at the wrist. This continues for some time and as the interval from the tub increases the pulse becomes softer and more flabby. The character of the pulse immediately before is in marked contrast to that after the bath. The one is soft, flabby, easily compressed and relaxed, while the other is usually firm and hard.

During convalescence the pulse-rate gradually drops and may show remarkable variations. Any little exertion or excitement may increase the rate from 20 to 50 beats a minute as seen in some patients when they begin to get about. This may continue for some weeks and as a rule is not serious, although it should suggest caution in letting patients do very much. Slowness of the pulse may be present during convalescence. This is by no means uncommon and the cases seem to fall into two groups. In one the slowness is not constant but is seen perhaps only during the morning hours of each day, when the rate may be from 40 to 60 and later in the day rises to normal. This may continue off and on throughout convalescence. To such cases the term bradycardia can hardly be applied. In the second group we have the true instances of bradycardia, which is more frequent after typhoid fever than any other acute infection. The pulse may sink to 40 or even 30 beats a minute and is usually small. This slow rate may continue for a considerable time and the return to normal be very gradual. It is perhaps most marked during the period of subnormal temperature so often seen during convalescence. With the bradycardia there may be irregularity or intermittency. In 117 patients a pulse-rate below 50 was noted during convalescence. In 6 a rate below 40 was noted, and the lowest, noted in 2, was 35. The fact that all of these patients recovered is significant and justifies the opinion that it is not a serious condition. Irregularity with bradycardia does not seem to be a serious sign.

Heart.—The heart cannot be said to show any changes peculiar to typhoid fever. The variations in the rate, character of the sounds, etc., may be due to several factors such as fever, toxemia, vasomotor paralysis with a secondary effect on the heart muscle, and myocardial changes. Dilatation may be present, but it is not often marked and is more common on the left than on the right side. With the progress of the attack the impulse usually becomes feeble and the apex beat may be diffuse or completely absent.

Heart Sounds.—These may be normal and unchanged throughout, as is seen in mild attacks, but as a rule some change is noted. The first sound usually becomes feebler and may have a muffled uncertain quality which may progress until it becomes inaudible. The second

sound may become sharper and more accentuated as the disease progresses. In 1125 cases of this series the heart sounds were clear throughout. In 333 (22 per cent.) murmurs were heard at some time. Of these, 16 were thought to be due to previous valvular disease and one was associated with exophthalmic goitre. Of the remaining 316 cases, the murmur was systolic in 312, diastolic in 1, and in 3 both systolic and diastolic. Of the cases in which a systolic murmur was heard, the situation was at the apex alone in 87, heard generally in 66, at the apex, tricuspid, and pulmonic areas in 49, at the pulmonic area alone in 35, at the aortic and pulmonic areas in 21, at the apex and pulmonic areas in 20, and the remainder in various associated areas. Of the 244 cases with a systolic murmur at the apex, this was present on admission in 199. The murmur was observed during the first three weeks in 85 per cent. The murmur persisted through the attack and was present on discharge in 31 out of 138 cases in which the point was carefully noted. The majority of these systolic murmurs were undoubtedly due to relative dilatation but probably some were associated with endocarditis.

Endocarditis.—This is one of the very rare complications and large autopsy records give few instances, only 5 per cent. in the Munich statistics. It was present in 6 cases of this series, in 3 of which it was discovered at autopsy and in 3 the diagnosis was made clinically. The mitral, aortic, and tricuspid valves have been involved. Instances of malignant endocarditis have been reported. Typhoid bacilli have been obtained from the vegetations and aortic endocarditis has been produced experimentally in rabbits by the intravenous injection of typhoid bacilli. In the 3 cases of this series staphylococci were obtained. The clinical features are in no way peculiar, but in making the diagnosis of endocarditis the occurrence of a relative insufficiency must be kept in mind as a source of error. A leukocytosis is in favor of endocarditis. Subsequent examination should make the diagnosis certain.

Pericarditis.—This is also very rare and was present in 3 cases. In one the patient was admitted on the ninth day with a well-marked rub which persisted for a week, and with this there was a bronchopneumonia. Later there was slight pericardial effusion. In the others the pericarditis appeared in the fourth week. In the two patients who were conscious there was severe precordial pain. Death followed in one and typhoid bacilli in pure culture were obtained from the pericardium.

Myocarditis.—To lay down definite rules by which this condition may be recognized is not possible. Rapidity and irregularity of the pulse, gallop-rhythm, embryocardia, a feeble impulse with marked change in the character of the first sound or its becoming almost inaudible, may all be considered as suggestive signs. Yet these may depend on vasomotor paralysis, and the changes in the myocardium occur secondarily. The appearance of a systolic murmur is suggestive of myocarditis but may be due to other causes. The changes noted in convalescence, either in the way of marked rapidity or of slowing of the pulse-rate, occasional intermittency or irregularity, suggest myocardial changes.

Reference should be made to the instances of sudden collapse which occur at the height or toward the latter part of the attack. Milder

grades may occur with some exertion, such as straining at stool, but these are rarely serious and of short duration. In another group the collapse appears suddenly and death follows rapidly. The condition of the myocardium or severe vasomotor disturbance may explain some of them. The symptoms are usually those of collapse; the patient looks very ill, the face pale and drawn, dyspnœa and sweating may be present, and with these a pulse which is very rapid and felt with difficulty. Death may follow in a short time, stimulation not being of the slightest use. Such conditions may occur after signs of cardiac weakness or may come on without the slightest warning.

Blood Pressure.—The routine record of the blood pressure is of considerable value but this must be taken throughout the attack to be of any help in the estimation of the patient's condition or in the recognition of complications. The pulse rate would be of little help to us if we took it only when the condition became serious or complications occurred. As a rule the blood pressure record should be taken twice a day; in severe attacks it had better be taken every four hours, while with the onset of suspicious abdominal symptoms it should be recorded every quarter of an hour while there is any doubt as to the condition. For ordinary work, if systematic records are taken, only the systolic pressure is necessary. The ordinary systolic pressure early in the disease varies from 115 to 125 mm. Hg. There is usually a gradual fall until at the end of the febrile period the pressure averages 100 to 110 mm. Hg. Two or three weeks after the beginning of apyrexia the pressure has usually returned to normal.

Arteries.—Acute complications during the course are uncommon but, as Thayer has shown, conditions may be set up which lead to the development of a considerable grade of sclerosis. Of the acute conditions aortitis has been described but is probably rare. There was no instance in this series. Fresh atheroma is not uncommon, but gives no clinical symptoms. The most important condition is arteritis, which occurred in 4 patients of this series—in 1 in the middle cerebral, in 2 in the femoral, and in 1 in the brachial artery. It is a matter of doubt whether or not arterial thrombosis occurs without a previous arteritis, but the evidence at present suggests that this is rare.

The symptoms of arterial thrombosis usually appear late in the disease. If in one of the vessels of the extremities, the first complaint is usually sudden severe pain along the course of the artery. With this, marked local pain and tenderness are associated; redness and swelling, with perhaps slight increase in the size of the limb, usually follow but as a rule with little or no œdema. Soon there is marked diminution or disappearance of the pulse in the artery peripherally; the extremity becomes cold, bluish in color, and the surface may be somewhat mottled. Following this, one of two things may happen. (*a*) The condition gradually shows improvement; the pulsation returns; the extremity regains its natural temperature and color and is practically restored to normal. Recovery is probably due to the collateral circulation, although channels may be formed through the thrombus. In some there is slightly less pulsation and some slight disability in the affected extremity.

Unfortunately this favorable result is not the rule, and we are more likely to have (*b*) the development of dry gangrene. This is usually ushered in by an increase in the coldness and discoloration of the limb. It may affect only the peripheral parts or extend up to the site of the thrombus.

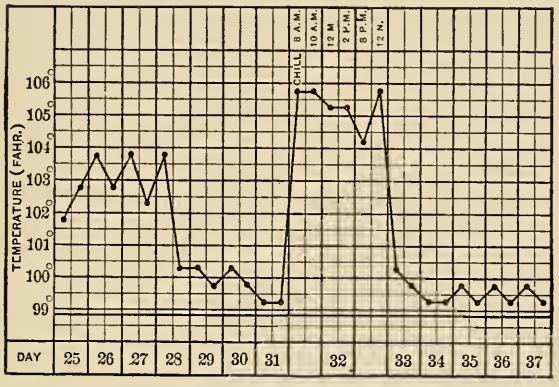
The above description applies to the cases in which arterial thrombosis occurs in the vessels of the extremities. When in the cerebral vessels, coma and convulsions with a sudden termination may follow. Some of the instances of aphasia and hemiplegia may be due to this complication. Whether in the cerebral vessels or in those of the extremities it is exceedingly serious. Pulmonary embolism may be a cause of sudden death.

Veins.—Complications occur in these much more frequently than in the arteries. Conner has emphasized the frequency of phlebitis in the smaller veins and suggests that it explains certain cases of indefinite pains. Among 8356 cases from the London Fever Hospitals thrombosis occurred in 171 (2 per cent.). In this series there were 41 instances (2.7 per cent.) with the following distribution: femoral 23, popliteal 5, iliac 5, veins of the calf 5, internal saphenous 3, common iliac 1, axillary vein 1. In distinction to arterial thrombosis a great majority occur in the veins of the leg; thus in this series the site was in the veins of the arm in 1, and in the veins of the leg or in the iliac in 40. There is always a preponderance on the left side. In this series thrombosis was on the left side in 28, on the right side in 5, and on both sides in 8 patients. The onset is usually in the third week or later, about half of the cases occurring in the third or fourth week. In about one-third of the cases, thrombosis appears after the temperature is normal. The first symptom is pain which varies a good deal in its severity and mode of onset. In the femoral vein it is usually referred along the course of the femoral vessels but sometimes lower down in the leg. In iliac thrombosis there is usually sudden sharp abdominal pain and, as this may be associated with tenderness and leukocytosis, perforation is suggested. In thrombosis of the lower veins of the leg the pain is usually referred to the vein but in some there may be indefinite pains in the calf. Even in femoral thrombosis, pain may be referred to the calf for two or three days before there are any definite signs.

There is usually some fever with the onset, either an increase in the previous temperature or a reappearance of fever if it has been normal. In only 3 of this series was there absence of fever. In a considerable number a chill occurs, as in 11 of this series (Fig. 9). As a rule there is some œdema, except in rare instances in which the saphenous vein and deep veins of the calf are involved. The swelling is often evident in the femoral region in femoral thrombosis before there is any œdema of the leg. There is frequently some local redness over the affected vessel. In a considerable number the thrombotic mass can be felt as a palpable cord. Although instances of detachment of a portion of the thrombus are rare it is well to bear in mind that the thrombotic mass should be palpated as little as possible. Leukocytosis occurs in the majority, the highest count in this series being about 35,000. Of the cases with thrombosis, 5 resulted fatally but only 2 as a result of the

thrombosis—one with axillary thrombosis from pulmonary embolism, and the other with thrombosis in the left iliac vein from embolism of the inferior vena cava and right auricle. While in many instances the process is probably due to a local condition in the wall, associated with the presence of typhoid bacilli, yet in others there may be a second infection. Thus in 7 of this series some other condition was present, such as boils, otitis media, etc.

Fig. 9



Chill at the onset of thrombosis.

Conner considers that thrombosis is probably much more common than we have supposed, and this is supported by the number of cases with pulmonary or pleural conditions apart from bronchitis perhaps due to embolism. In the majority of these the emboli are small and the condition is rarely serious. He draws attention to the fact that phlebitis and thrombosis may be the source of pulmonary embolism before showing any local symptoms. In a series of 29 cases with definite signs of phlebitis and probably embolism, pain was present in all and cough in the majority. Bloody sputum in small amounts was noted in about half the cases. In some cases there was a chill; the temperature varied. Some of these patients had multiple attacks. The physical signs are classified as follows: (1) A group in which a friction rub or crepitant rales over a small area were the only signs, lasting perhaps two or three days. (2) Cases with the signs of pneumonia, the evidence of consolidation disappearing in a few days; these were usually in the lower lobe. (3) Cases with extensive pleurisy or pleural effusion. These included more than half the cases. He also suggests that "tender toes" may be due to phlebitis of the veins in the region of the heel with secondary extension to the adjacent plantar nerves.

While not serious as regards the prospects for recovery, thrombosis causes a great deal of annoyance, discomfort, and sometimes considerable suffering. It may greatly lengthen convalescence. Gangrene may occur but is rare. The subsequent history often shows that thrombosis leads to more or less permanent disability, depending largely on the

vessel affected and on the extent to which the collateral circulation can be established. In probably every instance of thrombosis of the larger vessels there is some permanent change. The persistent swelling, especially after use, and the formation of varices are both very annoying. The varicosities may be associated with ulceration. There is often marked weakness of the affected limb and sometimes troublesome muscular cramps, especially after overexertion.

Of the causes of thrombosis we know little. That mechanical factors are important is evident from the unequal distribution in the two femoral veins. It seems probable that a local phlebitis is the cause of many of the cases. This is not necessarily followed by a complete plugging of the vessel, and it may be that phlebitis without much thrombus development is more common than is usually supposed.

Blood.—The blood shows important changes. At the onset and for the first two weeks there is little change in the red cells but usually in the third week a diminution in their number appears which goes on as long as there is fever. The number of red cells may be temporarily increased by profuse sweating, diarrhœa, or vomiting. A sudden loss may occur with hemorrhage. As a rule the average loss of red cells is about 1,000,000 per cmm. There is generally a drop in the hemoglobin, which as a rule is reduced more than the red cells proportionally and returns more slowly to normal. The appearance of many of the patients who have passed through a severe attack gives no accurate idea of the condition of the blood as they look more anemic than they really are.

Leukocytes.—The changes in their number are of considerable importance. As a rule the number is diminished and this decrease is to some extent progressive with the severity and duration of the disease. There is a certain degree of individual peculiarity and it is well to know the usual number of leukocytes, especially if the leukocyte count is to be of any value in the diagnosis of complications. There is naturally a certain normal variation but in uncomplicated cases they rarely reach 10,000 per cmm., and 4000 or 5000 may be regarded as about the average. The baths, especially at a lower temperature (70°), may cause a temporary increase. In the differential count the most marked change is an increase in the mononuclear elements and with this the polymorphonuclears and eosinophiles are decreased. With temporary increase in the number of leukocytes, as with the baths, the relative proportions remain practically the same. In severe attacks, especially with a protracted course and marked toxemia, the leukocytes may gradually decrease until they are 1000 or even lower. This steady drop with severe toxemia is usually of grave import. The usual low count is an important aid in diagnosis. It assists especially in excluding septic conditions, and in a patient admitted with abdominal symptoms suggestive of appendicitis the leukocyte count is most helpful.

The most important conditions under which leukocytosis occurs may be grouped as follows: (*a*) Various septic processes, such as furunculosis, abscess formation, etc., are nearly always accompanied by leukocytosis, which may even follow abrasions of the skin. (*b*) The various inflammatory complications, such as pneumonia, phlebitis, cholecystitis, etc.

(*c*) *Hemorrhage.* This is frequently followed by leukocytosis, which begins very soon after the bleeding and reaches its maximum as a rule within twenty-four hours. (*d*) *Perforation.* Safe conclusions from the leukocyte count can be drawn only if there have been careful counts beforehand. It is also essential that with the onset of symptoms counts should be made every hour. If they are made at intervals of four hours, a slight leukocytosis lasting for only two or three hours may be completely overlooked. The various changes in the leukocyte count with perforation may be grouped as follows: (1) Preperforative leukocytosis may occur but is probably very rare. (2) There may be no increase or even a diminution after perforation. Repeated counts are necessary before one can be certain of this. Such a condition suggests either a very severe infection with marked prostration or that the peritonitis is of a malignant type. (3) There may be a slight leukocytosis lasting for only two or three hours and then a rapid return to normal for that patient or even below the normal. (4) Marked leukocytosis may occur, and this may show a steady increase from hour to hour. Such an increase is not necessarily due to perforation and may be some other acute condition. In others there may be a fairly marked leukocytosis which remains at about the same point. The association of leukocytosis with the degree of infection does not follow any rule, but in general terms it seems true that with a severe, acute abdominal infection, especially with streptococci, the leukocytosis is not likely to be marked.

Late Effects on the Circulatory System.—The view has been gaining ground that typhoid fever may cause more permanent changes in the vascular system than was formerly thought. Thayer[1] has studied this in 169 patients of this series. Examination of the heart showed that the average size was greater than in the same patients on admission to the hospital. In 12 patients, who were discharged with apparently a normal heart, evidence of organic disease was found, 8 of these having mitral insufficiency with hypertrophy. Of 31 patients who had a systolic murmur during the attack, 20 had a murmur which in 5 was evidently of mitral insufficiency and in 1 of mitral stenosis. In the other patients a diagnosis of organic disease could not be positively made. The radial arteries were palpable much more frequently in the individuals who had had typhoid fever than in a control series, the figures being 48 and 17 per cent. This was supported by the observation that in a study of the frequency as to the palpability of the radial arteries, of 843 patients in whom the radials were felt, nearly 20 per cent. gave a history of typhoid fever, while of 231 who had not palpable radials only 10.8 per cent. gave a history of the disease. One patient who had arteritis in the left femoral artery showed enlargement of the affected leg and gave a definite history of intermittent claudication.

Observations on the systolic blood pressure showed that the average in those who had typhoid fever was uniformly higher than in those who had not had the disease. These all suggest that in certain patients typhoid fever does permanent damage to the vascular system.

[1] *American Journal of the Medical Sciences*, 1904, cxxvii, 391.

The subsequent condition of the veins was noted in 9 patients who had femoral thrombosis during the attack. In all there had been more or less disability and the affected leg was larger than the other. In 6 there had been œdema for varying periods and in the same number there had been pains in the legs, especially at night and after exercise. In all there were marked varicosities, which in 6 extended to the epigastrium. In 2 patients who had double iliac thrombosis, there were extensive varicosities over the abdomen, thighs, and legs. After thrombosis of the popliteal vein there was enlargement of the affected leg, and after involvement of the veins of the calf there was enlargement and in one patient œdema with varicosities.

Nervous System.—The manifestations in the nervous system are most important and interesting. There are very few patients who escape without some nervous manifestations and of these headache is the most common. It is a frequent early symptom which may persist throughout the attack or disappear during the second week. It may be referred to one area, often the frontal or occipital region, while in others it is described as a dull, heavy pain felt especially in the vertex, and in some patients it may have a marked neuralgic character, affecting especially the orbital nerves. The headache is often made very much worse by noise or movement. It may continue throughout the course but in the majority, as the general features of the disease become marked, the headache lessens or no complaint is made of it. Epistaxis sometimes relieves the headache.

There are certain symptoms, most common early in the disease, which may be referred to the nervous system. These include indefinite pains in the back and sacral regions, general malaise, with at times roaring in the ears, dizziness, and vertigo. Insomnia is sometimes marked early in the attack. As the disease progresses there is usually some dulness and stupor which may be of a very varying character. The patient lies quietly, apparently normal mentally, but when questioned it is evident that there is some delay in cerebration and difficulty in answering anything which involves a test of memory. There are all grades between this and a condition in which the patient is either actively delirious or in coma vigil. There are certain patients in whom instead of stupor there is a condition of marked alertness. They are usually keen mentally and their sensory perceptions very acute. This applies especially to hearing and should be kept in mind, as these patients may hear remarks made some distance away from the room.

The patients usually go along in a fairly comfortable condition; they doze and wake without much difficulty; they are easily aroused for nourishment and readily fall asleep again. In this group it may be difficult to estimate the mental condition. Thus a patient may be to all appearances clear mentally and yet when the attack is over have no recollection of events which have occurred. Examples are seen in the visits of friends or of a consultant. The patient may recognize a visitor and converse with him but later have no recollection of it. This is of importance in regard to business affairs or the making of a will. There are instances of patients, who mentally were apparently perfectly normal, making a

will and after the attack having no memory of it. The majority have little idea of time.

The degree of stupor varies greatly; it may be slight and perhaps most marked toward evening or through the night. These patients often show restlessness, try to get out of bed and wander about. The gentle restraint of a draw-sheet is often enough to prevent this. The condition may progress farther so that the patient lies in a dull state, taking no notice of his surroundings and oblivious of what is going on about him. It is usually possible to arouse them, although no intelligent replies may be obtained to questions. It is difficult to arrive at any clear idea of the mental processes in such states. If the patients can be made to talk it is doubtful if the information obtained is of much value. In rare instances they will give accounts of fantastic dreams and sometimes wake up out of sleep apparently much alarmed. At times there may be marked irritability and the patients complain of the nurses and attendants, resenting everything which is done for them. Great self-control is necessary in handling such patients, as their actions and statements may be very annoying. Children often show marked irritability and whine and cry almost constantly when awake.

A distinction has to be made between stupor and sleep. The patient who is apparently quiet and sleeping may be only in a dull condition and may go for days without any sleep. The extreme grade of this condition is termed coma vigil, a state in which the patient lies quietly, with open but unseeing eyes, sometimes seeming to follow the movements of those about him but really quite oblivious to his surroundings. These patients sometimes make an effort to talk but the result is usually a meaningless jumble of words. While in the majority the tendency is toward stupor yet in a number the delirium is of a more active character. This may be of all grades. The patients may be restless, active and noisy, with periods of special excitement. Their various impressions are apparently acute and sometimes of an alarming nature. Many are on the borderline between delirium and a psychosis. Individuals react very differently to fever and toxemia; very neurotic patients may be easily upset and certain persons become "flighty" with even slight fever.

Psychoses.[1]—These occur more frequently with typhoid fever than any other acute disease. It is convenient to follow the classification of Kraepelin, who divides them into (*a*) the initial delirium, (*b*) febrile psychoses, and (*c*) asthenic psychoses.

(*a*) *Psychosis at Onset.*—This is not common but as a rule is severe and patients have been committed to asylums under the idea that they were insane. In other cases they wander away in a dazed state and perhaps are found long distances from home, quite unable to give any account of themselves. This may be termed a confusional state. In others the features are more like those of mania. These patients are often violent, attempt to escape from their surroundings, and are

[1] There is no general acceptation as to what should be considered a psychosis in typhoid fever. Some writers regard every instance of delirium as a psychosis, while others hold that febrile delirium does not imply this. The subject has been considered by Farrar, *American Journal of Insanity*, 1902, lix, 17.

prevented with difficulty from injuring themselves. In this group are many of the instances of patients who crawl into freight cars, barns, etc., and remain concealed for days. These early manifestations are likely to occur in individuals who have a psychopathic tendency. The patients belong to two classes, one showing the features of a maniacal state, the other of more or less confusion. The prognosis in the first group is grave, death occurring in a large percentage; changes have been found in the cortical cells.

(*b*) *Febrile Psychosis.*—This is the largest group. The etiological factors are probably two—fever and toxemia. Different writers ascribe a varying degree of importance to each of these. While fever may be largely responsible for mental features, yet from a clinical standpoint one is impressed by the importance of toxemia as seen in patients without high fever but very toxic. On the other hand, some patients show a marked improvement in the mental state with any drop in temperature. The definite psychoses, as Farrar says, show no distinct clinical type but have only the specific etiology. They are very various and difficult to classify but may be divided into (1) conditions associated with hallucinations, which by some writers are described as partial or acute insanity, (2) maniacal delirium, and (3) stupor.

1. In this group come what may be regarded as the most typical examples of psychoses. Among these there are many instances of patients having curious ideas about their bodies. An example of this was seen in a patient who had been at times delirious and rather restless. One day he was found in great distress because he thought he had lost both his arms. He held up his hands to show the stumps and nothing that could be done with his hands would convince him that he still had them. In his condition it was not possible to determine definitely the state of sensation in the hands. Some of these ideas may be very grotesque. One patient imagined that all his abdominal viscera had been removed, which naturally gave him extreme distress, but with convalescence this idea gradually disappeared. In some, delirium would not be suspected unless all the circumstances are known, as shown by an intelligent woman who had done a certain amount of nursing. She had a moderate attack and was apparently perfectly clear mentally. She complained of rather severe abdominal pain, which was relieved by stupes, and she had a comfortable night. Next morning she gave a most detailed, circumstantial account of having had an ttack of appendicitis and of the operation which had been performed during the night. She gave the name of the surgeon and his assistants, with details of what they had said to her. When an attempt was made to examine the abdomen she begged us to be careful not to disarrange the bandages. She seemed so clear mentally and told the story with so much detail that anyone seeing her for the first time would have accepted it as true. In a few hours she realized that she was mistaken and had imagined the whole story, but for some time whenever she was a little confused, as after waking from sleep, the ideas would return.

The frequent occurrence of these conditions in the colored patients is striking and they furnish a relatively large proportion. In many the

delusions are especially associated with their occupation. In some cases the disturbance may be associated with the idea of getting out of the hospital. In others there may be periods during which the patient is in an exalted mental condition alternating with periods of depression. These seem to be more common toward the end of the attack.

2. Maniacal delirium may occur during the course and a patient who seemed previously unable to lift his head from the pillow may show remarkable strength.

3. The condition of stupor needs no special description. The patients may lie perfectly quiet or in a muttering delirium. From the words which can be understood it may be evident that they have delusions of various kinds. Others may lie quiet and refuse to take any nourishment. This is usually most marked after the febrile period. These febrile psychoses may terminate with the fever or persist into convalescence. Belonging to the first group are the majority of those which are associated directly with the fever and toxemia. In the majority the duration is not more than a week. Only a very small number, given by Kraepelin as 3.2 per cent., last for a year.

(*c*) *Asthenic Psychoses.*—It is easily seen how favorable the time of convalescence is for the development of a psychosis. The long duration of fever and toxemia, the marked emaciation, anemia with or without hemorrhages, all favor the development of mental changes. Kraepelin divides this group into three: (1) Isolated delusions or fallacious sense perceptions, (2) conditions of exaltation, and (3) conditions of quiet depression, including states of mental weakness. An example of the first group was seen in a patient who during the fever thought he had been arrested and sent to jail, where he supposed he was. The outlook in these cases is favorable; with the improvement in the general condition the psychosis usually disappears.

The second group includes various forms. Thus in one instance there was acute delirium with marked exaltation which occurred after hemorrhage. Sometimes the patient shows more or less exaltation which continues for some time during convalescence. In others there is a state of depression in which the patient lies perfectly quiet and with this there may be hallucinations. The outlook is always serious, especially when there is difficulty in feeding the patient. The outlook in this group is probably less favorable than in the febrile type, although the large majority recover. The history before the attack, as regards heredity, etc., is probably an important factor. Mental symptoms may appear some time after the attack.

As regards the frequency of permanent mental changes after typhoid fever, there is considerable difference of opinion between the clinicians and the alienists. It is natural that the latter should be more impressed by its frequency than the former. Edsall in discussing typhoid insanity has pointed out that the cases are more common than has been generally supposed, but it is difficult to give any positive statistics. It has been noted that if a patient with previous mental disease goes through an attack of typhoid fever, the mental condition may be greatly improved.

There are certain conditions which are difficult to classify. In many

patients after recovery there is a state usually termed "neurasthenia," which varies all the way from a hypersensitive irritability to depression very close to melancholia. This may quite unfit a man for any work, as there may be loss of memory, irritability, and a tendency to mental fatigue or confusion after very slight exertion. If the patient persists in endeavoring to work there will soon be marked fatigue and considerable depression. It may be months or even years before complete recovery occurs in such a case. These seem more likely to appear in individuals who had a neurotic tendency before the attack and are undoubtedly favored by too early a return to work.

The condition of the memory is interesting. Early in the attack the patient may have almost entire loss of memory so that a history is obtained with difficulty. During the height of the fever there may be almost complete loss of memory even when the patients are apparently not delirious. When convalescence begins the majority of the patients find that the memory is much impaired. This may be for names, dates, and previous occurrences as well as for events which happened during the illness. This is frequently a great worry to patients, but as a rule the restoration is complete although slow. In some patients there may be hysteria or hypochondriasis and with these marked depression. The term mental insufficiency well describes some of these conditions. Occasionally they may pass into more serious mental states.

Hysteria.—Manifestations of this are not uncommon. The patients lie quietly with the eyes shut and refuse to speak, or have typical hysterical attacks associated with crying and noisy demonstrations. When examined, they assume a look of intense suffering associated with patient resignation. Others may complain of attacks of severe pain. In some there are emotional attacks associated with rapid sobbing respirations. Some of them may be very noisy and scream loudly until exhausted. Others may show frequent rhythmical movements, more especially of the jaw. With these there may be areas of hyperesthesia, especially over the abdomen. This complicates the diagnosis, especially in patients with abdominal pain, but the recognition of the superficial tenderness is of great help. In other patients there may be marked hysterical dyspnœa or aphonia. A condition closely allied is catalepsy, which occurred in two patients of this series. There are usually associated hysterical features and the patient will keep the arm or leg in one position for some time. With this he may lie with the eyes shut, apparently oblivious of his surroundings. The condition is generally of short duration.

Tetany.—This, while a very rare complication, may occur and has been reported as especially prevalent in certain epidemics. There was no instance in this series.

Tremor.—In some degree this is very common and varies from the simplest tremor to conditions which might almost be termed a convulsion. It may occur early in the disease in irritable individuals or alcoholics. During the height of the disease it is usually an indication of the degree of toxemia. Slight tremor of the tongue is common and of no special significance. There may be tremor of the lips and irregular twitching of the muscles of the face. More serious are the irregular

muscular twitchings usually seen most markedly in the arms and trunk. This may be fairly general or involve certain muscles and tendons, the so-called subsultus tendinum, while in others there may be irregular movements of the hands and picking at the bedclothes. Other patients will often pick at the clothing of anyone coming near them, a very common trick being the attempt to take hold of the buttons on one's coat, or the stethoscope, while the patient is being examined. In other cases there may be frequent rapidly repeated movements, especially of the arms. Sometimes there is trismus and a condition almost like tetanus. All these occur without any organic lesions. There may be quite marked tremor after the attack is over. This usually disappears with increasing strength, but there are instances of its being permanent.

Meningitis.—In some patients at the onset the nervous symptoms may be so prominent that meningitis is suspected. The delirium, retraction of the head and rigidity of the neck may suggest meningeal involvement. Later in the course the same symptoms may appear. In the recognition of these conditions lumbar puncture is of the greatest help. The cases in this series have been studied by Cole, who divides them into three groups: (1) Those with symptoms of meningitis in which no lesions were found or no relationship between the bacteria and the symptoms; this has been termed *meningism.* (2) Those in which the typhoid bacillus was found in the cerebrospinal fluid but without any lesions of a suppurative character; these may be termed serous meningitis. (3) Cases of purulent meningitis.

1. This group should be described as typhoid fever with meningeal symptoms rather than typhoid meningitis. It is difficult to exactly limit the cases belonging to this group. Its recognition is important, as it may lead to a wrong diagnosis. It is important to remember that all the clinical features of meningitis may be present. Kernig's sign may be well-marked apart from meningitis, as in 8 of the last 685 cases of the series. It is important to keep this in mind, as certain writers make the statement that Kernig's sign never occurs in typhoid fever apart from meningitis. In this series the diagnosis of this group was made either by the negative findings of lumbar puncture or by autopsy. It may be noted that well-marked ankle clonus was present in two.

2. *Serous Meningitis.*—In this there is a mild grade of inflammation associated with changes in the meninges, which are microscopic and consist of œdema and round-cell infiltration about the bloodvessels. The exudate is serous and usually contains typhoid bacilli. Cole found 8 cases in the literature and reported 5 from this series. There is usually headache, mental dulness and either unconsciousness or delirium. Convulsions occurred in 4 of the reported cases, while stiffness of the neck and retraction of the head were frequent but not constant. In 2 cases facial paralysis occurred. Kernig's sign was present in 2 cases and absent in 2. The reflexes showed considerable variation. In none of the cases was there a leukocytosis. Death occurred in all the patients of this series but one, but this was not necessarily due to the meningeal conditions. The most important point in the recognition is the result of lumbar puncture; in all the reported cases the fluid was clear and

only a few leukocytes were found; the amount varied from 20 to 60 cc. Typhoid bacilli were grown from the spinal fluid in all. The pressure did not seem greatly increased, but the removal of the fluid seemed to improve the condition.

3. *Purulent Meningitis.*—In this group there is a definite purulent meningitis associated with the typhoid bacillus. Cole collected 13 cases in the literature which he considered authentic, and there was 1 case from this series. The symptoms show no special difference from those of the serous type. The onset may be early or late but death as a rule follows within a few days. Delirium, muscular rigidity, and incontinence of urine were marked features, but in only 1 case were convulsions noted and in only 1 did paralysis develop. Priapism may be present. Kernig's sign was absent in the case of this series and also in 2 out of the 3 other cases of purulent meningitis and in 3 out of 5 cases of serous meningitis. The spinal fluid contained enormous numbers of typhoid bacilli and many polymorphonuclear leukocytes. Other organisms may set up purulent meningitis; tuberculous meningitis has been observed, as in one patient with the serous type in whom typhoid bacilli were obtained from the spinal fluid during life, and at autopsy fresh tuberculous meningitis was found. Meningeal hemorrhage is not common, but small circumscribed hemorrhages may cause focal lesions.

Cerebral Lesions.—These are not common. Hemorrhage, thrombosis, embolism, meningo-encephalitis or abscess may occur, sometimes in convalescence, and following them there may be areas of softening. It is difficult in many of the cases reported without autopsy to decide with certainty the character of the lesion. Aphasia has occurred in a certain number, at times associated with right-sided hemiplegia. There are some cases which may have been due to minute emboli, but in others it probably occurred without an organic lesion. Bulbar paralysis has been noted and there are a few cases of abscess. Hemiplegia occurs during the course or in convalescence. The condition shows no special peculiarity. Paraplegia is not common. Gowers mentions that some patients never seem to be able to walk as well after an attack of typhoid fever. Monoplegias have been reported, but there is always a suspicion that they are instances of neuritis. There are cases reported as having general choreic movements but there is always the possibility that they were true chorea. Instances of paralysis agitans coming on after typhoid fever are described.

Spinal Lesions.—These like the cerebral are comparatively rare. Myelitis may occur and in a case reported by Curschmann was definitely associated with the typhoid bacillus. Poliomyelitis has been observed in some instances secondary to typhoid fever.

Reflexes.—They may be exaggerated or entirely absent and this variability is seen in ordinary attacks or in those with meningitis. The state of the reflexes may vary from day to day. Kernig's sign and ankle clonus may be obtained in patients who have no organic lesions.

Convulsions.—These are extremely rare, there having been only 7 instances in this series. They may occur under various conditions: (*a*) At the onset, especially in children. (*b*) During the course and probably

as a result of the toxemia. These are not common and the toxemia is only suggested as a possible explanation. (*c*) A group due to cerebral complications, such as embolism, thrombosis, hemorrhage, etc., which are always serious. (*d*) In convalescence. It may not be possible to give any explanation, although in some instances they are due to hysteria. (*e*) With other conditions, such as *epilepsy* or *uremia*. An epileptic who has typhoid fever may have his usual convulsions, although generally they occur rather less frequently during the fever. The instances of convulsions due to epilepsy are not included in the 7 cases noted above. Convulsions are always serious, not from any danger in the convulsion itself but because they may be due to a serious cerebral complication. Of the 7 cases in this series 3 died. It has been suggested that in some they are due to œdema of the brain or to local vasomotor changes.

Neuritis.—This is not common and occurred in 11 cases of this series, or 0.7 per cent. This does not include the instances of tender toes. Neuritis may occur during the latter part of the disease or in convalescence. It may be either multiple or local.

Multiple Neuritis.—As a rule this comes on during convalescence. The four extremities or the legs may be involved. It may be difficult to diagnose from poliomyelitis and it is probable that some of the cases in the literature put down as spinal disease are really neuritis. Some instances of multiple neuritis are regarded as due to the alcohol given during the attack.

Local Neuritis.—This may come on during the attack but more commonly with defervescence and convalescence. The pain is often very severe and there may be great tenderness on pressure over the nerve, with marked wrist or foot drop in some cases. In others there may be marked swelling of the affected limb and considerable circulatory disturbance. The conditions which may result are very various; thus there may be quite marked contractures, atrophy, curious trophic disturbances, chronic contractions of the muscles and sensory disturbances. Meralgia paresthetica has been reported as a sequel. In other cases there is considerable tenderness which is rather ill-defined but increased by pressure on the muscles. This also suggests myositis rather than neuritis. In all such cases the possibility of phlebitis must be kept in mind.

Tender Toes.—This may come on during the height of the attack or in convalescence but is rarely seen early. The toes, especially their plantar surface and occasionally the adjoining part of the foot, become extremely painful. The patients usually complain first of the pain caused by the pressure of the bedclothes, but it often increases so that they cannot bear any weight or the gentlest touch. The pain rarely lasts more than a few days in a severe form. Examination is practically negative and there is no redness or swelling. It is said that the condition is more likely to occur in patients who have had the baths, but it may occur after an attack so mild that no hydrotherapy was necessary.

Special Senses.—*The Eye.*—The ocular complications have been especially studied by Bull and de Schweinitz. Catarrhal conjunctivitis occurs during the febrile period, especially in severe attacks, and is probably associated with the decrease in secretion. Keratitis is rare;

iritis, choroiditis, and inflammation of the vitreous have all been noted, while cataract has been observed in a few cases. Retinal hemorrhages are said by Bull to occur fairly often, and may be part of the manifestation of the hemorrhagic type. Embolism is extremely rare. Double optic neuritis has been noted, which may occur with meningitis or as a local process. Hemorrhage into the optic nerve is rare. Hyperemia of the fundus, papillitis and dilatation of the retinal vessels have been observed. Optic nerve atrophy has been noted. Paralysis of both the intra- and extra-ocular muscles may occur, and there was one instance in this series of paralysis of the extra-ocular muscles which came on early in the attack. Slight local meningitis seems the most reasonable explanation. Ptosis has been observed. Amblyopia has been noted rarely. Thrombosis of the orbital veins has occurred but is rare.

The Ear.—Excluding conjunctivitis, affections of the ear are much more frequent than of the eye. Early in the disease there may be subjective disturbances, the patient complaining of roaring in the ears. Deafness without any discoverable lesion occurs comparatively frequently. It may occur at the onset or during the course, and may appear suddenly or develop gradually during two or three days. In some patients it may be difficult to decide whether deafness or stupor is the more important condition, and in those who are deaf the lack of attention to questions has been ascribed to stupor. The explanation of deafness is difficult to give, but the subsequent course shows it is usually not a neuritis. As a rule recovery is complete but in some the disturbance may last during convalescence and occasionally it may be months before hearing is restored. Such cases and those with a permanent loss of hearing suggest a neuritis, although a local meningitis may be the cause. As a rule the outlook is good and the patient is left with the hearing unimpaired. Otitis media is quite common and its frequency varies greatly from year to year. Hengst among 1228 cases found it in 29 (2.3 per cent.) and in this series it occurred in 21 patients (1.4 per cent.). It is usually not serious, although it may extend to the mastoid. In this series there were several patients with redness and swelling over the mastoid without any otitis, but in no case was operation necessary. The organism present is usually one of the pyogenic cocci. In no cases of this series was the typhoid bacillus found in the discharge, but there are a few instances in the literature. In some patients the otitis may appear during convalescence and be the cause of an elevation of temperature.

The Nose.—Special disturbances are rare. Some patients complain persistently of disturbed nasal sensations, and smell a foul odor not perceptible to others.

Renal System.—In this are changes due to the febrile state, which show no special difference from those due to any fever, and also those peculiar to the typhoid infection. The specific gravity as a rule is increased and the reaction is strongly acid during the height of the attack, later often becoming neutral or alkaline. The amount of urea and uric acid is increased and may be double the normal, while the chlorides are decreased. This description has to be altered if large

amounts of water are given, for if the amount of urine be increased to three liters or more *per diem*, the color is pale, the specific gravity much lower, 1015, 1010, or even less, and the reaction is very feebly acid, neutral or alkaline. If large amounts of urine be passed, such as six or more liters, the specific gravity may fall even lower, to 1001 to 1005, and the color be very pale. The investigations of Sollman and Hofmann on such cases showed that the eliminating capacity of the kidneys was not injured. There was no accumulation of fluid in the body and the total chloride secretion was increased. Diuretics did not increase the amount of urine.

Polyuria.—It should be the endeavor to produce this in every patient. In patients who are not being given this "washing-out treatment" a sudden polyuria may be observed, usually toward the end of the attack, although it may appear at the height of the fever.

The statistics of albuminuria vary greatly. Thus Curschmann gives 15 to 20 per cent., but in this series albumin was present at some period in 999 cases (66 per cent.). Casts were found in 568 cases (37.8 per cent.). In a large number albumin was found only during the first few days after admission. Thus, among the last 685 cases, in 175 albumin was found only on the first four days after admission and was not present afterward. In many of these it was found only during the first day in the hospital. This is not peculiar to typhoid fever, being seen in other febrile conditions. Albumin in the urine is ordinarily due to two causes, (*a*) the febrile state, and (*b*) changes in the kidney. It is difficult to decide the number of each but in the great majority it is due to the former. In 150 others of the last 685 cases the albuminuria persisted through a considerable part of the attack.

The amount of albumin varies but in many is a mere trace, especially when present for a short time only. Tube casts may be found but are usually scanty. The duration of albuminuria is rarely more than ten days, although in some patients, what was regarded as febrile albuminuria persisted throughout the greater part of the attack. Severe anemia may be a cause.

Among the special conditions is the onset with acute renal features, the *nephrotyphus* of the Germans or *forme renale* of the French. There was only one instance in this series. It is regarded as a serious condition.

Pigments.—There may be marked increase of the pigments. Urobilin and indican may be found in large amounts but it is doubtful if either has any special significance. Patients with large amounts of indican in the urine may have mild attacks with no special features. The increase of indican is not of importance in the recognition of the onset of peritonitis, nor does it mean any special intestinal condition.

The Diazo Reaction of Ehrlich.—The reaction was given in 61 per cent. of this series. The frequency of its occurrence is much diminished if the patients are passing large amounts of urine, or if present the reaction may be given very feebly. In such it may be obtained by evaporating the urine down to a quarter of its bulk. Its value for diagnosis is slight, as it occurs in other diseases, such as malarial fever and acute tuberculosis. The reaction depends on incompletely oxidized

products of nitrogenous metabolism which belong to the aromatic compounds. Acetone is often found in the urine (12 per cent. in some series) and β-oxybutyric acid occasionally. The excretion of phosphates is diminished during the attack and increases with defervescence. The methylene blue reaction described by Rosso has no special value.

Bacilluria.—This term in typhoid fever is usually applied to the presence of typhoid bacilli in the urine, although strictly speaking it includes any organism. The incidence of bacilluria varies with the epidemic but especially with the care with which the urine is examined. In many patients the condition is transient, only a few bacilli may be present, and without frequent careful examinations these will be missed. It seems reasonable to state that bacilli are present in the urine in from 20 to 25 per cent. of all cases. The routine administration of hexamethylenamine reduces the incidence.

Bacilluria does not seem to be associated with the severity of the attack and in this probably lies a great danger in the spreading of infection. The number of bacilli varies; there may be only a few or they may be so numerous that the urine has a distinctly turbid appearance. This is sometimes so characteristic that the diagnosis can be made at a glance by holding a test-tube full of urine up against the light, when a curious shimmer is seen. The number of bacilli in the urine has been estimated as sometimes amounting to several hundred thousand millions *per diem.* The explanation of their occurrence is difficult. That they are derived from the bacilli in the blood, being passed out, as it were, does not seem an adequate explanation as the periods of greatest frequency in the blood and urine do not correspond. Nor does it seem probable that local conditions in the kidney can be a frequent cause. Direct passage through the bowel and bladder wall is a possibility but probably does not occur frequently. In some cases their presence may be due to local processes in the bladder or prostate. The suggestion made by Horton-Smith that they are derived from stray bacilli which reach the bladder and there find conditions favorable for multiplication, seems the most likely explanation.

Bacilluria does not necessarily cause any symptoms unless cystitis occurs. The presence of actively motile bacilli in freshly voided urine is very suggestive. Cultures are necessary to render the diagnosis certain, and care must be taken to differentiate the organism from the colon bacillus. Bacilli rarely appear in the urine before the third week and may be found for the first time in convalescence. With bacilluria there may be albuminuria, pyuria, or cystitis, but they are not necessarily associated. In addition to the typhoid organism the colon bacillus and various cocci may be found. Bacilluria may persist for many years.

Pyuria.—This occurs in a number of cases but the percentage varies with what is considered pyuria. In many patients a few pus cells may be found but such can hardly be included under this term and in females only the examination of catheterized specimens can be considered. Pyuria does not usually give rise to any symptoms, and it is not necessarily associated with pyelitis or cystitis. The possibility of gonorrhœa

being the cause has to be kept in mind. The gonococcus and typhoid bacillus may be together in the bladder.

Hematuria.—As a rule this is associated with conditions in the kidney, although the frequency of changes in the mucous membrane of the bladder suggests that in some cases these may be the source of hemorrhage. Hematuria is of importance only as indicating other conditions. Hemoglobinuria is a rare and serious condition, present in two cases of this series. In a case reported by Musser and Kelly there was hemoglobinemia with the hemoglobinuria.

Acute Nephritis.—This may occur at the onset—nephrotyphoid—and quite conceal the true condition. It is often difficult to separate febrile albuminuria from slight nephritis and one may pass into the other. On this account it is difficult to state the frequency of acute nephritis. In this autopsy series it was present in 8 out of 105 cases, in 2 of which it was hemorrhagic. Curschmann puts the incidence at scarcely 1 per cent. In the clinical series 10 patients were regarded as having acute nephritis. There are rarely any symptoms suggestive of uremia, and œdema is uncommon. As a rule if the patient recovers, the renal condition clears up completely and acute nephritis rarely becomes chronic. There has been no such case recognized in this series. Chronic nephritis was found at autopsy in 6, having been present before the attack of fever. Nephritis during convalescence is rare.

Pyelitis.—This may occur during the height of the disease or in convalescence and may be difficult to distinguish from cystitis. There may be blood and pus in the urine at first, the pus continuing. Severe pyelonephritis may occur but perinephritic abscess is rare. The diagnosis of pyelitis may offer considerable difficulty. In some patients during convalescence there is a sudden increase in temperature with pain referred to one kidney. Tenderness on palpation in the region of the kidney, a sudden increase in the amount of pus in the urine, accompanied in some cases with a little blood, and possibly a marked leukocytosis, suggest acute pyelitis. The condition usually clears after a few days. A definite pyelitis was found only once at autopsy and typhoid bacilli in pure culture were obtained. Colon bacillus infection is not infrequent. In rare instances there may be a post-typhoid pyelitis with ulceration, erosion, and the formation of a diphtheroid membrane, which may be associated with a similar condition of the bladder.

There are rare renal conditions such as lymphomatous nephritis, infarcts, abscesses, etc., which are of no special clinical importance. Multiple abscesses were found at autopsy in 7 cases.

Cystitis.—Its frequency is difficult to state. The diagnosis was made in 32 cases of the series (2.1 per cent.). In patients who have bacilluria it is difficult to draw the line between pyuria, slight catarrh of the bladder, and a true cystitis. Cystitis may be due to the typhoid bacillus but also to the colon bacillus or staphylococci. The cystitis offers no special features. Some patients have practically no symptoms, or there may be pain with frequent and painful micturition. Cystitis may be the cause of persistent fever. As a rule cystitis due to the typhoid bacillus improves much more rapidly under treatment than when due to the

colon bacillus. Acute cystitis was found at autopsy in 4 cases, not including the cases of hemorrhage into the mucous membrane of the bladder, which are comparatively frequent.

Prostate.—Abscess of the prostate was found once at autopsy. Prostatitis and inflammation of the seminal vesicles may be due to the typhoid bacillus. The persistence of bacilli here may cause bacilluria after recovery.

Urethritis.—This has been noted in rare instances apart from a gonococcus infection. No direct proof of its being caused by the typhoid bacillus has been found.

Retention of Urine.—This is often troublesome and is quite common at the onset, when it may be partly due to the difficulty in urination which many patients have for the first day or two after they are kept in bed. Later in the disease it may be associated with stupor, and in such patients the utmost care should be taken to prevent retention, for if distension occurs the patient is rarely able to void. If retention has occurred there may be no complaint from the patient, but on examination of the abdomen there is a well-marked swelling in the hypogastrium, which may extend up to the navel. The passage of urine does not exclude retention, as there may be constant dribbling from an overdistended bladder. Incontinence is most frequent in patients who are dull and stupid, and may be associated with distension. The patients should be waited on frequently, but if this is not effectual some form of urinal or bag should be used.

Reproductive System.—Gangrene of the genitalia is rare in males, although there are cases in which the penis and scrotum were involved. In the female it is much more common, and Keen reported 17 cases. The process may involve the external genitals or the vagina and cervix. It may extend to the perineum or cause fecal fistulæ. Suppuration of the glands of Bartholin has been noted, associated with the *B. typhosus.*

Ovary.—Abscess of the ovary has occurred and the typhoid bacillus been found in the pus. Abscess in a tube has also been observed, as in a case reported by Scudder, with the typhoid bacillus in pure culture. Hemorrhage into the ovary has been found at autopsy. Fullerton[1] has drawn attention to the importance of the typhoid bacillus in pelvic inflammatory conditions and pelvic abscess. In several cases it has occurred in association with another organism.

Menstruation.—As a rule this ceases during the disease, although at the onset it is not uncommon for menstruation to occur, often with a short interval since the preceding period. During the course of the disease it was present in 11 among the 438 female patients but not with the profuse flow which some writers consider common when menstruation does occur. In the hemorrhagic type, bleeding may occur from the uterus. Menstruation may be a cause of abdominal pain. In patients in whom there is a possibility of pregnancy, hemorrhage due to abortion should not be mistaken for menstruation. It may be some months before menstruation reappears after the attack.

[1] *Surgery, Gynecology, and Obstetrics*, 1913, xvi, 180.

Pregnancy.—Among the 438 female patients in this series there were only 6 who were pregnant (1.4 per cent.). Abortion or premature labor occurs in the majority. Thus of 169 cases with full data collected by Sacquin pregnancy was terminated in 103. Of these, 124 were less than seven months pregnant, of whom 72 miscarried, and 45 were over this period, with premature labor in 31. Lynch concluded that typhoid fever was more often seen in the first half of pregnancy, and that pregnancy was most likely to be interrupted in the third month and in the second week of the fever. Miscarriage occurred in 5 of the 6 patients, the sixth being delivered subsequently of a living child.

The typhoid bacillus may pass from the mother to the child in utero, usually in cases with hemorrhagic lesions in the placenta. The child apparently always dies of the typhoid septicemia but does not necesarily show intestinal lesions. The agglutination reaction is not always given by the fetal blood, and if present it may come from the mother's blood or may have been due to changes arising in the blood of the fetus.

Puerperal infection with the *B. typhosus* may occur. There have been 3 instances in the obstetrical department of the Johns Hopkins Hospital. In one there was a localized lesion in the chorion from which the bacilli were obtained in pure culture.

Glandular System.—*Mastitis.*—This is rare and occurred in 4 of this series, 3 being females. In about half the cases in the literature both breasts were involved. Suppuration occurred in about half the cases and in a few instances the typhoid bacillus has been obtained from the abscess or by puncture of the inflamed gland. Mastitis may appear during the attack, usually after the third week or in convalescence. In one patient both breasts were involved during the attack and one for the second time in a relapse. There is usually pain, swelling, and tenderness of the breast with elevation of temperature. Leukocytosis is common. The condition does not have any unfavorable influence. Slight induration of the breast occurs frequently; the patient may not complain of pain. It is of no importance and rarely lasts long. Pain may be present without any induration.

No authentic instance of the occurrence of typhoid bacilli in the milk has been found. The agglutination reaction may be given by the milk and was given by the colostrum of one pregnant patient on the seventeenth day, while the blood serum gave it on the twentieth day, when typhoid bacilli were obtained by blood culture. The agglutination reaction may be given by the blood of the nursing child, apparently having been conveyed by the milk.

Orchitis.—This is not frequent and was present in only 4 cas s of this series (0.27 per cent.). As a rule it appears late in the disease or in convalescence. It may come on with a chill, and if the temperature has fallen there is usually marked elevation. In one patient it occurred at the beginning of a relapse. As a rule the testicle is affected first, the epididymis later; the swelling may be marked and the pain is usually severe. In the majority the condition is unilateral. In a certain number suppuration has occurred (in 29 out of 69 cases collected by Blumenfeld), and in some of these typhoid bacilli were obtained. The duration is

usually from twelve to eighteen days, and induration or atrophy of the testicle may result.

Thyroiditis.—This is not an uncommon condition in some localities and is said to be relatively frequent in Switzerland. It is apparently more common in patients who have enlargement of the gland. It did not occur in this series. The symptoms are pain, tenderness, and some enlargement of a part or whole of the gland. Dysphagia may occur, especially if the left lobe is involved. The process may clear up entirely or terminate in suppuration and the organism may be the typhoid bacillus or one of the pyogenic cocci. Thyroiditis is most likely to appear in the latter part of the attack or during convalescence. As a rule it is not dangerous, although in a few cases there have been serious symptoms from pressure.

Lymphatic Glands.—General enlargement of these may occur but has no special significance.

Osseous System.—Lesions of the bones are more common after than during the attack. In all the lesions the organism most frequently found is the typhoid bacillus and sometimes in pure culture in the fluid obtained by aspiration of the swelling of periostitis. In a few the pyogenic cocci are present, while occasionally the cultures are sterile.

Periostitis.—During the course of the disease this is the most common osseous lesion, although it may appear in convalescence or months after the attack. Its frequency varies greatly; thus among 8356 cases in the London Fever Hospital there were 110 (1.3 per cent.) but only 8 instances in this series (0.5 per cent.). It occurs most frequently in the ribs, clavicle, or bones of the extremities. The symptoms are pain, tenderness, and swelling, with redness over the affected area. There is rarely any constitutional change. The process may subside and recur later, there may be thickening which persists for some time, or abscess formation may follow.

Bone Lesions.—The most common lesion is necrosis, then caries, osteitis, and osteomyelitis. It is rare for them to appear during the course; they are more frequent afterward. The only instance in this series early in the attack was in a boy, aged ten years, who had fluctuating masses on the frontal bone and on one rib. The former contained greenish pus, cultures from which were negative; the latter subsided without interference. The time between the attack and the onset of bone lesions may be many years, intervals of six and seven being reported. Practically any of the bones may be affected but the majority of cases occur in the leg. There is rarely any fever or constitutional disturbance except in very acute cases, and in the majority the old term of "cold abscess" applies. Pain, tenderness, swelling, and sometimes redness are found locally. As in periostitis the course is variable; the process may subside or there may be a recurrence but more commonly there is abscess formation, and if pus is present the condition is likely to become very chronic. If a sinus form or a partial operation be done, suppuration may continue indefinitely and typhoid bacilli persist for years. In some cases there may be a sequestrum present. In rare cases the process extends to the adjoining soft parts or to a joint. This tendency

to chronicity and recurrence suggests the necessity of thorough treatment; no half measures are effectual. The outlook is usually good, although there may be danger in the cases of mixed infection.

Typhoid Spine.—This term is used to describe a group of cases in which, usually toward the end of an attack or during convalescence, certain symptoms appear which are referred to the spine. Attention was first directed to it by Gibney in 1889. It usually follows a mild attack and the majority of those affected are males. In a few instances the symptoms apparently follow trauma. The onset is rarely longer than three months after the attack. Pain is the most prominent symptom, is usually in the lower dorsal or lumbar region and may radiate around the body or down the legs. It is variable and may be very severe on movement. There may be difficulty in walking, and bending of the spine may be impossible. Swelling of the soft parts, kyphosis and scoliosis have been noted. Rigidity and fixation of the spine, sometimes associated with tenderness, may be found. The reflexes may be altered and symptoms referable to the nerve roots are common, such as severe pain, muscle spasm and cramps, wasting, disturbances of sensation, etc. Fever has been present when the condition occurred in convalescence. The duration varies from weeks to many months and relapse has occurred.

The condition is a spondylitis which is proved by the *x*-ray plates in some cases. In two patients (one with a typhoid, the other with a paracolon infection) definite deposits of new bone were shown in the plates. These are reported elsewhere.[1] In some patients neurotic features are so marked and the evidences of any organic changes so slight that a functional disturbance is suggested. Others complain of pain in the back for months after the attack without having the features of typhoid spine. These, with the instances of persistent weakness of the legs for a long time after an attack, may be examples of slight grades of spondylitis.

The cases can be classified under three heads: (1) Those in whom the nervous features predominate and in whom no organic changes can be found. There is no disturbance of temperature or pulse; the patient may declare that he cannot move his legs, which he does a few minutes later when his attention is directed elsewhere; there may be disturbances of sensation. Certain other patients who complain of pain in the back which may persist for months should perhaps be put in this class; the symptoms are not severe and they are usually able to get about without difficulty; some of these suggest mild varieties of typhoid spine. Others have persistent weakness of the legs for a long period and may belong to this group. While the general neurotic features are prominent it is impossible to exclude slight changes in the spine. (2) Periostitis or perispondylitis. The occurrence of fever, pain, rigidity and evidences of nerve-root involvement, all suggest a local process. Gibney regarded this as a perispondylitis, "meaning an acute inflammation of the periosteum and the fibrous structures which hold the spinal column together." It can readily be seen that even extensive inflammatory conditions may not give any positive local sign of disease. (3) A group with definite

[1] *American Journal of the Medical Sciences*, 1906, cxxxii, 878.

changes. It may not be proper to separate these from the former group, as they probably always follow the changes mentioned there.

The diagnosis rarely offers any great difficulty, but the decision as to the exact condition present may not be easy. A previous spondylitis should be excluded. The radiograph should be of help in recognizing the cases with organic bony changes, and in every case of "typhoid spine" plates should be taken. Tuberculosis of the spine is not likely to give much difficulty. The local pain may be so severe that abscess formation may be suspected. The outlook is good, recovery being the rule. There may, however, be pain and tenderness for months or, in some, years after. Some disability and slight rigidity may persist and relapse may follow strain or injury.

Arthritis.—This is rare and was present in only 8 cases of this series, 4 being monarticular and 4 polyarticular. It usually arises spontaneously, but in rare cases it may be due to the extension of a bone lesion. There is pain, swelling and redness which may persist throughout the attack. Suppuration and permanent ankylosis are rare. The tendency to dislocation, especially in the hip-joint, must be remembered. Keen found that spontaneous dislocation had occurred in half the reported cases, the majority being in young persons. It usually occurs with serous distension of the joint in convalescence. In rare cases the exudate is purulent and a sinus may form. The frequency of dislocation in the hip-joint suggests care in watching for the onset of arthritis, and if it appears every effort should be made to prevent dislocation. Except for this the outlook in arthritis is good.

The Muscles.—Degeneration is of more interest pathologically than clinically, for symptoms are rarely observed. Hemorrhage may occur into the substance of the muscle, and should this become infected, abscess formation follows. Rupture is rare and no instance occurred in this series. In the majority it is late in the disease, generally in males, and often thought to be due to movements in delirium. The symptoms are sudden pain and tenderness. There is usually a hematoma, and suppuration often follows. The typhoid bacillus has been found in the pus. The complication is a serious one because it usually occurs in severe attacks. In some instances suppuration in the abdominal muscles has extended to the peritoneal cavity, so that it is well to open freely as soon as suppuration occurs in this situation. In some patients there is a condition seen during convalescence which suggests a myositis. There is tenderness on handling or pressing the muscles which may continue for some weeks but usually gradually disappears. Phlebitis and neuritis must always be excluded.

Abscesses.—No part of the body in which abscess may occur is exempt. The typhoid bacillus is the causal organism in a varying number of cases depending on the site of the abscess. In other cases the typhoid bacillus and other organisms—usually the pyogenic cocci or colon bacillus—are associated or these organisms occur alone.

1. Abscesses in the skin, subcutaneous tissues, muscles, bones and connective tissues are common, especially if boils are included. They usually appear late in the disease or during convalescence. If they

appear as sequelæ the suspicion of a periostitis being the cause should be considered. Abscesses may be situated anywhere, perhaps most frequently about the buttocks. In some regions, as about the neck, they may arise by extension from one of the glands or from the larynx. They may even extend to the mediastinum. Alveolar abscess is not uncommon, especially in connection with carious teeth, and is of some gravity as a general secondary infection may occur. As a rule abscesses heal rapidly after incision.

2. In the viscera: These are rare but have been noted in every organ.

3. In the glands: Any of these may be the seat of an abscess, especially the parotids, submaxillary glands, thyroid, breast, and testicle.

4. In the abdominal cavity: Here there may be a great variety of curious abscesses. After perforation, especially in the ileocecal region, adhesions may wall off the abscess cavity and perforation take place later into the bowel or externally. It is a question whether such abscesses may occur without perforation of the bowel but this seems possible. Subdiaphragmatic abscess is rare. In one patient with perforation and general peritonitis a large abscess was found between the right lobe of the liver and the diaphragm. Abscess may follow suppuration in a mesenteric or retroperitoneal gland. Pelvic abscess may occur, either by extension from the tube or from perforation in the rectum.

Gangrene.—This is not a common condition. Keen collected 133 cases in his monograph. It is not necessarily found in severe attacks only, many of the reported instances having occurred during a mild course. The cases may be classed under the following heads: (1) Superficial gangrene of the skin. (2) In association with bed-sores. This is usually due to pressure but in some cases apparently occurs in areas not especially exposed to this. It occurs rarely about the heels. (3) In association with conditions in the arteries. Plugging of the arteries may be due to embolism or thrombosis, the latter more frequently. The gangrene from this cause is of the dry variety and usually occurs in the extremities. (4) With venous thrombosis. This is rare, considering the frequency of thrombosis. The gangrene is of the moist variety. (5) A group of cases with gangrene occurring in various superficial areas, seen especially about the genitalia and perineum, especially in women. Other areas, as the lips, ears, tongue, uvula, etc., are sometimes involved. Noma has occurred rarely. There are a few instances of gangrene of the lung. An area of gangrene on the abdominal wall has followed the prolonged application of an ice-bag.

Duration.—The length of the attack varies greatly and no definite period can ever be set. The average duration in the last 500 cases of this series was 29.4 days of fever and 49 days from the onset until discharge from the hospital (those with relapse or perforation and the fatal cases not being included). This does not represent the length of stay in the hospital but the time from the onset of the disease, and the patient was not considered free of fever until the temperature was normal during the whole twenty-four hours. Among 73 patients with one or more relapses the average duration of fever in the original attack was 30.4 days and the average from onset until discharge 73.2 days.

Recrudescence and Relapse. — The term recrudescence is used for periods of fever of a few days and not accompanied by other signs, such as fresh rose spots. Return of fever due to a complication is not considered a recrudescence. A relapse must be characterized by at least two of the three important features of the disease, namely, a characteristic fever-curve, enlargement of the spleen, and rose spots. As a rule it is well to insist on an interval of twenty-four hours of normal temperature before the subsequent elevation, to justify a diagnosis of a true relapse. The term intercurrent relapse is used to describe those cases in which the temperature is dropping or has fallen perhaps nearly to normal and rises again, to remain elevated for some time.

Recrudescence.—The prominent feature is fever, which as a rule is not high and does not last for more than a week. The patient may feel just as well as before or complain of slight malaise and headache. The cause of these elevations may be excitement, too much exertion, solid food, constipation or a slight attack of diarrhœa. In some patients it has been coincident with the appearance of typhoid bacilli in the urine or a pyelitis and careful search should always be made for these when an otherwise unexplained elevation of temperature occurs. In the last 685 cases there were 18 regarded as recrudescence and in 3 of these there was also a relapse. The average duration of fever was about one week. The longest interval of normal temperature before a recrudescence was sixty-two days.

Relapse.—This occurred in 172 patients in this series (11.4 per cent.). The figures given by different writers vary all the way from 3 to 15 per cent. and a collection of 28,057 cases showed 2493 of relapse (8.8 per cent.).[1] The number varies from year to year and also in different localities. We can lay down no positive rule that a certain period of apyrexia must occur before the use of the term relapse is justified, for the general features must always be taken into consideration. In some cases it seems perfectly justified to make a diagnosis of relapse after only a few hours of apyrexia, although usually there should be an interval of twenty-four hours of normal temperature.

The Ordinary Relapse.—The average period of apyrexia between the original attack and the relapse is about 6 days and the longest interval in this series was 43 days. There seems little doubt that the predisposition to relapse is greater after a mild than after a severe primary attack and the mildest cases may be followed by a very severe relapse. After a severe primary attack a relapse is usually milder than the original. The onset may be very sudden, with a chill and high fever, and complications, such as orchitis, glossitis, or phlebitis. Enlargement of the spleen seems to persist after defervescence in a large number of patients who later have a relapse. The pulse-rate sometimes rises before the temperature. The symptoms do not differ especially from those of the primary attack, although as a rule the pulse is more rapid in the relapse, and dicrotism is said to be less common. Hemorrhage and perforation are apparently much less common in relapse, there being only 2 instances

[1] Statistics of Curschmann, Gerhardt, Liebermeister, Murchison, Brand, Hare, J. McCrae, London Fever Hospital, and the present series.

of hemorrhage and 1 of perforation among this series. As a rule the course is more favorable than in the original attack, for among 172 cases of relapse there were only 5 deaths (2.9 per cent.).

One group deserves special mention—that in which the duration of the relapse may be very long or more than one relapse occur. There are a number of instances reported with five relapses. In these protracted cases the duration of the disease may be almost a year.

Intercurrent Relapse.—This is fairly common, although it may be difficult at times to say whether or not the diagnosis of intercurrent relapse is justified. We can usually make it when the temperature has been falling but is not down to normal and suddenly goes higher and continues elevated. These attacks may be protracted and severe and are responsible for many of the cases which drag on for months. The symptoms are not especially different from the ordinary attack, except that severe features may be present for a long period. In others there may be little but the fever, which sometimes seems as if it would continue indefinitely. At times a patient may have a moderate or even slight attack without high fever, and at the end of the third week the fever becomes higher and all the symptoms are more severe. It is doubtful whether such instances should be included under this term. In some patients, especially after a protracted course, the temperature may fall to normal and then for several weeks run along at about 100° to 101°, and with this there may be no special features. It is hardly correct to term this a relapse. Care should always be taken not to mistake a secondary infection for a relapse.

The explanations given for relapse are not very satisfactory. It may occur when the bactericidal power of the blood is highly developed and may be then due to certain strains of bacilli having greater resistance and so being able to multiply. But the whole matter is so involved with the difficult problems of immunity that many points must be left for future explanation. The occurrence of relapses suggests that more than the bactericidal power of the blood or the neutralization of specific endotoxins is concerned. For a time it was regarded as a reinfection but this is contrary to the behavior of acute infections generally. The gall-bladder was considered to be a source of infection and the early giving of solid food, causing an increased flow of bile, was thought to explain certain instances in which the relapse seemed to be determined by dietetic errors. But this can no longer be regarded as satisfactory, especially when we consider how frequently the bacilli must persist in the gall-bladder, not to speak of other localities. The explanation that in relapse cases there is special involvement of the large intestine is not supported by autopsy records. Durham has suggested the most satisfactory explanation. Infection is the result of the action of a sum of number of infecting agents which are similar but not identical, so that there may be a number of varieties and subvarieties. If the members belonging to different varieties are nearly equal we have a "normal or isozymic" infection, in which no unit predominates, each is affected equally by the antibodies, and no relapse results. However, if one variety predominates we have an "abnormal or anisozymic" infection

and there may be but small protection against one form, which may begin to multiply rapidly and cause a relapse. In connection with this the finding of both the typhoid and paratyphoid bacillus in the one patient may be noted.

Second Attack.—In a series of 500 cases this point was specially studied and a definite history of a previous attack was obtained in 11 (2.2 per cent.). The interval between the two attacks was nine months in 1, ten months in 1, from one year to ten years in 4, and over ten years in 5 cases. The longest interval was thirty years.

Varieties.—Different forms of the disease have been described and in some the most marked symptoms have been fixed on, so that such names as pneumotyphoid, nephrotyphoid, etc., came into use. It does not seem advisable to use these designations, as they lead to confusion. The symptoms in one system may be especially prominent at the onset and the same may occur during the course. It is convenient to separate certain varieties but it is to be understood that cases do not necessarily conform to any of these.

1. Malignant Typhoid Fever.—The mode of onset is usually very sudden with high fever early in the attack, or more gradual with severe prodromal symptoms. This variety seems likely to occur in young adults who are stout and well-nourished. From the onset the symptoms are severe and there is often marked toxemia with signs of cardiac weakness. The patients sink into the characteristic typhoid state, the pulse becomes rapid and weak, distension of the abdomen occurs frequently, diarrhœa may be present, and the fatal termination may come before the end of the second week. Death is usually from severe toxemia, hemorrhages may occur but are not common. In such fatal cases at autopsy the intestinal lesions are usually not far advanced and their extent does not correspond to the severity of the clinical picture. The prognosis is grave and from the onset the outlook is serious.

2. Mild Typhoid Fever.—This is an exceedingly important group, especially as regards prophylaxis, for these very mild attacks may not be recognized and the patients are the means of spreading the disease. The cases may be divided into two classes, the first including those characterized by a mild and short course, the other those in which, despite the short course, the onset is severe. To this latter group the term of *abortive* typhoid is often applied, for although the attack begins with severe manifestations, these suddenly disappear, the temperature soon falls, and the course is short. In epidemics, certain patients may have slight fever, perhaps with diarrhœa, lasting only for a few days.

The recognition of this group comes through one of two ways. They may show characteristic signs, such as rose spots, or be recognized only through the routine Widal reaction. In mild attacks the rose spots may not appear until after the temperature is normal, and if there has been no suspicion of typhoid fever it is not likely that careful search would be made for them after the fever has disappeared. Sometimes the diagnosis may be made only by a relapse or the appearance of some complication. The relapse is commonly more severe than the original attack. In other instances it may be the onset of phlebitis that suggests

the diagnosis. The routine Widal reaction has been of great service in the recognition of this group; the older statistics cannot be regarded as being as accurate as those made since its employment. In the group with a sudden severe onset but a rapid defervescence the duration may be comparatively long and certain organs show marked involvement.

We are not sufficiently impressed with the importance of this group. Keeping their frequency in mind, the physician will watch more closely and have the agglutination reaction tried more frequently in patients with mild fever. It is easy to use every means of diagnosis to clear up a doubtful severe infection or at any rate there is the stimulus to do so, whereas in a mild fever with rapid recovery and the patient well it requires energy and a strong sense of duty to do it. Even the patient may not appreciate what seems to him needless enthusiasm and care, still for him it may be a safeguard when we recall instances of a fatal relapse after a patient has returned to work, which gave the diagnosis with unfortunate certainty. For the community the recognition of this group is most important and many instances of infection are probably due to the mild unrecognized attacks.

How mild may a typhoid infection be? During epidemics persons may complain of symptoms which persist only for a few days and there is the suspicion that such may be instances of very mild infection. The occurrence of typhoid bacilli in the stools of individuals who are apparently perfectly healthy is important in this connection. These mild attacks may be compared to those seen during an epidemic of cholera, in which infections of very varying severity are found.

3. Ambulatory Typhoid Fever.—This term is variously used and some confusion has arisen as to its meaning. It is sometimes applied when the symptoms are so mild that the patient hardly feels ill enough at any time to go to bed and may be at work throughout the entire attack. It is likely that a number of such cases are never recognized, as shown by the fact that patients who have kept at work throughout the original attack occasionally come with what is evidently the beginning of a relapse. This type of case really belongs to the mild group. The other use of the term is to describe the group in which the patients have fought the disease and kept about on their feet. This is seen especially among laborers, sailors, etc., but also in the higher walks of life and not uncommonly in physicians and nurses, who may keep at work for days with high fever. The course is usually exceedingly severe and often within a few hours after going to bed the patients become delirious and show marked nervous manifestations. In others, hemorrhage or perforation may be the first thing that makes them give up.

4. Hemorrhagic Typhoid Fever.—This group comprises the cases in which bleeding occurs from various parts of the body. The term should not be applied to those with hemorrhage from the intestine only or to those with a petechial rash. It is rare and occurred in only 3 cases of this series, in 1 of which there were no intestinal lesions. Liebermeister noted it in 3 among 1900 cases, and Uskins in 4 among 6315 cases. Curschmann has seen 6 cases. It may be present in the malignant type, during the course of an ordinary attack, in the later stages or even in

a relapse, as in one of our patients. The bleeding is frequently from the nose, gums, and intestines and less often from the lungs, kidneys or uterus. Petechiæ frequently appear and may be seen between the rose spots, which do not necessarily become hemorrhagic. There may be bleeding into the tissues, and cerebral hemorrhage has occurred. In severe cases gangrene may follow.

We are unable to give any explanation of the cause; in some it is analogous to the hemorrhagic cases seen in other infectious diseases. In others it may be associated with a secondary infection, or it may be a cachectic manifestation. Rarely it may be due to the hemorrhagic diathesis or to the association of purpura hæmorrhagica with typhoid fever. The coagulation time is prolonged. The outlook is grave and the majority of the patients die—about two-thirds of those reported—although all in this series recovered.

5. Afebrile Typhoid Fever.—This is described and while it is not possible to deny that it occurs, still the cases must be very rare. Some of those described in several recent articles had slight fever for some days and really belong to the group of mild cases. In debilitated and old persons an attack may occur without any fever. There was no instance in this series.

Variations Depending on Condition, Race, and Age.—*Condition.*—As a rule fat patients do badly and we much prefer to have the lean type to deal with. Many believe that patients who have used alcohol freely are bad subjects. In regard to the station in life there does not seem to be any special difference between the upper and lower classes. In those who have suffered privation, the lack of care early in the disease is an important factor.

Race.—This is of interest in localities in which the colored race is present in large numbers. The colored patient seems less resistant than the white. The death-rate in this series among the colored has been practically double that in the white (15 per cent. in the colored and 7.8 per cent. in the white). The colored patients seem to "go to pieces" more easily and if they have intestinal hemorrhage or severe toxemia, especially with cardiac weakness, death may follow very rapidly. It has to be remembered that colored patients are likely to have had greater privation and less care before admission.

Sex.—No special difference is found as regards the sexes. The death-rate is about the same in large statistics. Men are more likely to keep about on their feet and be admitted with severer symptoms. Alcoholism is more common among them, while in the other sex pregnancy gives a somewhat greater risk.

Age.—This plays an important role. For the first two years of life the danger is comparatively great, from two to fifteen there is less risk, while after forty the danger is greater and increases with each year.

Typhoid Fever in Infancy.—Formerly regarded as rare, we have learned that typhoid fever during the first two years of life is not uncommon. The question has recently been studied by Griffith and Ostheimer, who collected 325 undoubted cases under the age of two and a half years. Of these, 111 were in the first year, not including the congenital cases,

of which they found 12 undoubted instances and quote 5 doubtful ones. The presence of the Widal reaction is not sufficient proof of the correctness of the diagnosis of congenital typhoid fever, as the agglutination may have passed from the maternal to the fetal blood through the placenta or after birth through the milk. Intestinal lesions appear to be rare in these cases. The death-rate is high and only 3 of the patients recovered. Of those in the first year recovery was noted in about 25 per cent. but it must be remembered that probably the diagnosis was not made in many instances of recovery. In the second year they found 171 genuine and 7 doubtful cases, with recovery in nearly 70 per cent. in which the result was given. Of the cases in the first half of the third year 28 per cent. died. In their series the males and females were equal in number. More than half of the cases occurred during general or house epidemics. A paratyphoid infection has been found in infancy.

The symptoms in infancy show some variation from those in adult life. The onset is more variable and nervous features, which may suggest meningitis, are prominent. Rose spots and enlargement of the spleen are apparently as common as in adult life, while hemorrhage and perforation are comparatively rare, probably due to the slight development of the intestinal lesions, with less tendency to deep ulceration. The duration of the attack seems to be shorter than in adults. The mortality of the published cases is high but the milder cases are often overlooked or not reported. Serious conditions sometimes follow recovery, such as deaf-mutism, aphasia, convulsions, and arrested mental development.

Typhoid Fever in Childhood.—This offers no special features, except that as a rule the course is mild and often atypical. The fever may not be high but the pulse-rate is often more rapid in proportion than in adults. Children are very apt to pick at the nose and lips, so that fissures and bleeding often occur. Distension of the abdomen is not uncommon. In very young children the symptoms may be much like those of colitis. Perforation appears to be rare up to the age of five years. Jopson and Gittings collected 2274 cases of typhoid fever in children with 35 cases of perforation. Adams found 17 cases of perforation in a series of 550 cases. There were 28 deaths in this series attributed to hemorrhage. These reports suggest that the disease in children is not as free from serious complications as is sometimes thought. In this series among 40 cases of perforation there were 4 in children under fifteen years of age. Children seem to do well after operation for perforation, 3 out of the 4 recovering. Among the complications and sequelæ, aphasia, mental changes, otitis and bone lesions are apparently more common than in adults. The duration of the fever is generally less than in adults and the mortality lower. Children are said to be more subject to relapse.

Typhoid Fever in the Aged.—As a rule, in advanced life the features are not so acute as at earlier periods. The patients are likely to show early delirium, usually of a low type, the temperature is not so high and often remittent. Frequently the pulse is rapid and cardiac weakness appears at an early stage. Severe bronchitis, bronchopneumonia, and hypostatic congestion are common. Enlargement of the spleen may

not be evident; hemorrhage is exceedingly grave in advanced life. If recovery follows, the convalescence is likely to be slow and protracted.

Typhoid Fever in Pregnancy.—The association is not very common and in this series among 438 female patients 6 were pregnant (1.3 per cent.), 5 of whom aborted. Considerable difference of opinion exists as to whether pregnancy gives a relative immunity against infection with the typhoid bacillus; certainly during the puerperium and lactation typhoid fever is comparatively rare. Abortion may occur early in the disease but in one of our patients it did not occur until convalescence. While adding somewhat to the risk, pregnancy with typhoid fever cannot be considered as being very serious. An attack during lactation does not show any special features. One patient admitted in the second week of a severe attack had nursed her child up to the time of admission; he had suffered from diarrhœa, which disappeared as soon as nursing was stopped, but his blood did not give a Widal reaction.

Typhoid Fever in the Fetus.—In a certain number of cases there is intra-uterine infection; the fetus shows a septicemia without internal lesions. This is not invariable, as there are instances in which the child escaped. The conditions which determine the passage of the bacilli from the maternal to the fetal circulation are not positively known but probably some disease of the placenta is necessary, and hemorrhagic infarcts have been found in several cases. When the fetus becomes infected death follows in the majority of cases but this is not invariable The presence of bacilli must be proved before a diagnosis is made.

Colon Typhoid.—Some writers have drawn attention to a group of symptoms found when the colon is specially involved. These comprise a fetid diarrhœa, marked meteorism, frequent hemorrhages, small in amount and of bright red blood, and a rapid downward course.

Association with Other Diseases.—Malarial Fever.—Perhaps the most important association is that of malarial and typhoid fevers, not for their actual coexistence but on account of the ideas as to the frequency which have existed in the minds of so many of the profession in this country. "Typhomalarial" or malarial typhoid fever" is the diagnosis frequently made of continued fever in some sections of the country. Three conditions are included under the term. (*a*) It is applied to patients with malarial fever who are in the "typhoid" state or who have a very severe infection. (*b*) A hybrid disease, formed by the union of malarial and typhoid fevers. This disease, non-existent in the patient, still finds an abode in the minds of many of the profession. This was the sense in which the term was used by Woodward, who introduced it in 1862. (*c*) The occurrence of the two diseases in the patient at the same time, which is the sense in which the term has been used by French writers especially. A fourth class might almost be added, owing to the habit many physicians have of diagnosing many obscure febrile affections as "typhomalarial" fever. It is to be hoped that the profession will cease to use the term. In mortality returns "typhomalarial" fever may be considered as practically always typhoid fever.

The actual association of typhoid and malarial fevers is rare. In this

series there were only 3 instances of combined infection. When the reported cases are studied it is seen that the malarial parasites were found in the blood during the fever of the typhoid attack in a very small number. In a large majority they appeared during convalescence, exactly as after a surgical operation or confinement if there has been a previous malarial infection.

Tuberculosis.—This association is of interest in many ways. Does typhoid fever predispose to tuberculosis? Does tuberculosis give a relative immunity against typhoid fever? This is difficult to decide by statistics, but when we remember the large number of individuals with tuberculosis the percentage who have typhoid fever seems small. The association may be considered as follows:

1. They may coexist and a patient with tuberculosis have typhoid fever. In this series a clinical diagnosis of pulmonary tuberculosis was made in 6 patients and at autopsy active tuberculosis was found in 7 cases, of which 2 were in the lung and 5 in the glands. One of the patients with tuberculosis of the mesenteric and bronchial glands had also a tuberculous meningitis, and one with involvement of the bronchial glands had Addison's disease. Evidence of old tuberculosis was found at autopsy in 9 instances, of which 5 were healed lung lesions and 4 chronic pleurisy. Miliary tuberculosis and typhoid fever may coexist.

2. Tuberculosis may follow typhoid fever. By some this is regarded as being by no means rare, but it is more probable that in the majority the diagnosis of typhoid fever was wrong and the condition tuberculous from the beginning. In some patients a previously existing focus may be stimulated to greater activity.

3. The diseases may be mistaken for each other. This is probably the most frequent association, one disease in the patient and the other in the mind of the physician. There are several forms which may lead to confusion.

(*a*) *Acute Miliary Tuberculosis.*—This mistake may be made even with the possibility of it in mind. As a rule the error is in mistaking miliary tuberculosis for typhoid fever rather than the reverse.

(*b*) *Tuberculous Meningitis.*—This may show symptoms suggestive of typhoid fever, especially if the patient is not seen from the onset, but the absence of the characteristic signs of typhoid fever and the results of lumbar puncture should give the diagnosis.

(*c*) *Tuberculous Peritonitis.*—If the patient has been seen from the beginning there is rarely confusion, but later, especially if the history be indefinite, they may be difficult to distinguish.

(*d*) *Glandular Tuberculosis.*—If this be accompanied by constant fever and toxemia the diagnosis may be very difficult.

(*e*) *Pulmonary Tuberculosis.*—If the fever be constant and toxemia marked there may be confusion, but a careful examination of the lungs should render the mistake unlikely.

In all of these a tuberculous condition is usually regarded as typhoid fever but the contrary mistake may be made, perhaps most commonly in patients whose attack begins with marked pulmonary or pleural signs.

When meningeal symptoms are prominent early in the disease the diagnosis of tuberculous meningitis may be made.

Acute Infections.—The coincidence of these with typhoid fever is relatively rare. As regards scarlet fever, Fournier in a recent review of the literature found 75 instances of the coexistence of this with typhoid fever. Typhoid fever may precede, which is the most common association; the diseases may occur together, as in an instance reported by Hektoen; or typhoid fever may occur after the attack of scarlet fever. Caiger among 48,000 scarlet fever patients in the London Fever Hospitals reports 11 as having typhoid fever associated. The prognosis of the typhoid fever does not seem any worse on account of the association. Smallpox, measles, chickenpox and whooping-cough have been observed. usually coming on in the latter part of the attack of typhoid fever. Typhus fever has followed the other disease, instances having been noted in which a patient with typhoid fever has been sent to a typhus ward and contracted the disease. Diphtheria may be seen, but the presence of the diphtheria bacillus is necessary for diagnosis, as a diphtheroid membrane may occur in typhoid fever. Some cases of coincident infection with the *B. typhosus* and streptococci have been reported, both typhoid bacilli and streptococci being found in blood cultures. These are usually very severe and run a rapid downward course. Influenza and typhoid fever may coexist; they may run concurrently or the influenza may precede the typhoid attack. Erysipelas is not common. Among 1635 cases of erysipelas, Anders found 2 associated with typhoid fever. Asiatic cholera and typhoid fever have been associated but usually one disease follows the other. Tetanus and anthrax have occurred with typhoid fever. Gonorrhœa and typhoid fever may coexist.

Gastro-intestinal Disease.—The occurrence of gastro-intestinal disorders apparently does not predispose to typhoid infection. Typhoid fever may occur in patients who have amœbic dysentery and Strong found 4 cases among 100 fatal cases of amœbic dysentery in Manila. During the attack of typhoid fever the amœbæ may not be found in the stools but reappear in convalescence. The severe intestinal features of typhoid fever may suggest dysentery, but the diagnosis should be made only if amœbæ or *B. dysenteriæ* are found.

Trichinosis. — Until 1862 these diseases were always confounded. There was one instance in this series of their association. Trichinosis may simulate typhoid fever very closely, as the general features, enlarged spleen, rose spots—although they do not come out in successive crops—and diazo reaction may all be present.

Chronic Diseases.—It has been thought that chronic nervous diseases and typhoid fever rarely coexist but this is probably not correct. Patients who have epilepsy usually have fewer attacks during the course of the fever. In patients with chorea the movements usually stop during the attack but may recur in convalescence. In some instances the choreic movements have been much exaggerated at the onset of the attack. Patients with hysteria or neurasthenia who have typhoid fever are often markedly benefited. In a patient with diabetes mellitus the excretion of sugar may diminish markedly or even disappear during the attack.

The association is usually regarded as having a grave prognosis and Curschmann points out that the temperature in these patients is often comparatively low. Typhoid fever may develop in a patient with cholelithiasis; in 4 of this series, gallstones were found at autopsy, in 2 being associated with malignant disease.

Malignant Disease.—Typhoid fever rarely develops in patients who have malignant disease and the difference in the ages of greatest incidence does not altogether account for this. In this series it occurred in 2 instances, one being carcinoma and the other sarcoma of the gall-bladder. In both the infection with the *B. typhosus* was a terminal one.

Syphilis.—This association is not rare. Some of the physicians in the South African War considered that in patients with syphilis who contracted typhoid fever the outlook was grave and the death-rate high.

Chronic Alcoholism.—Chronic alcoholics are usually bad subjects and show a very high mortality. They have slight resistance and are prone to serious cardiac manifestations, also being apt to show marked nervous manifestations with low delirium, marked restlessness and great prostration. Active delirium tremens does not seem to be very common in typhoid fever.

Appendicitis.—Its relation to typhoid fever is an important one.

1. One may be mistaken for the other. This is by no means infrequent; usually the patient with typhoid fever is thought to have appendicitis. The mistake of considering appendicitis to be typhoid fever is not likely if the patient has been seen from the onset but is possible if he is seen for the first time after an illness of some days especially if there be a small abscess. However, in the majority of such cases, careful examination should give the diagnosis without doubt.

2. Conditions in the appendix due to the specific typhoid lesions. The occurrence of ulceration in the appendix is comparatively common. It is easy to understand that with such lesions we may have acute symptoms. In some instances the attack of typhoid fever may be associated with changes in the appendix from previous inflammation. Changes secondary to the typhoid lesions may occur.

3. *Perforation.*—This may occur in the appendix as elsewhere and requires no special discussion. It is possible that perforation occurring in an appendix which is lying posteriorly is more apt to be walled off and cause a local abscess.

4. *Acute Appendicitis with Typhoid Fever.*—This is rare but does occur. There was one such instance in this series, the appendix being found acutely inflamed but without any evidence of a typhoid lesion.

5. *Appendicitis May Follow Typhoid Fever.*—This may be an accidental association or following the typhoid ulceration subsequent changes may be favored.

Intussusception.—Several instances of this have been reported, in one with hemorrhage, the diagnosis of perforation being made. Intestinal obstruction due to various causes may occur.

Associated Bacterial Infections.—These may be various. Thus infection with the pneumococcus and typhoid bacillus is usually present

when pneumonia is a complication. Both organisms have been obtained in blood cultures. The influenza bacillus may be obtained in the same way. Of the pyogenic organisms, streptococci may be associated early in the attack or streptococci or staphylococci later, sometimes from infection from bed-sores or boils. In some instances typhoid and paratyphoid bacilli have been obtained from the same patient.

Diagnosis.—The diagnosis has to be made from the clinical features or by laboratory methods. With a disease which shows so many variations in its symptoms and course it is evident that diagnosis by clinical methods may be difficult and made only at autopsy. There is no symptom or sign which is invariably present, and although fever may be said to be of almost constant occurrence, yet this may be of slight degree or more or less irregular. There are some general statements which may be made. Other diseases simulate typhoid fever more frequently than it simulates them, except when symptoms or signs are localized in one organ, as the "pneumotyphoid" variety. A good rule is to consider typhoid fever as a possibility in every doubtful fever, even if this be somewhat irregular. Again, the relative frequency of diseases is an important point. Typhoid fever is one of the most frequent continued fevers and if it be kept in mind the chances of overlooking it will be much less.

The onset is usually gradual. The patients can often tell quite definitely when the feelings of malaise first became marked, but after this there is rarely any change. In a small number the onset is sudden. The features of onset show no special peculiarity; general malaise, anorexia, and headache are common. The face often has a characteristic heavy, dull expression and the patient may show a suggestive slow mental condition. As a rule there is fever, although for some days this may be very slight and perhaps only after a week rises to the usual height. The occurrence of bronchitis is very suggestive; it varies greatly in severity and sometimes has distinctive features, the patient usually makes little complaint of it and while the cough may be severe there is rarely much sputum. The history of epistaxis is an important aid. The pulse may show two distinctive conditions, one dicrotism, which if found early is very suggestive, and the other a rate relatively much slower than that which might have been expected from the degree of fever. With this there is a furred tongue which shows tremor early and perhaps a heavy, foul odor to the breath. The bowels may be constipated or there may be diarrhœa, especially if a purgative has been taken, and if so the character of the stools may be suggestive. In the examination of the abdomen, enlargement of the spleen is important, although it is often present in other acute febrile conditions, especially influenza. The presence of rose spots is the most important point and these should be looked for every day, it being kept in mind that they may be found only on the lower thorax or on the back. There is often difficulty in determining whether doubtful spots are typhoid rose spots or not. In such cases it is well to mark a doubtful area and watch it during the next two or three days, when a decision should be easy. Abdominal distension is rarely present in the early stages. There is often slight tenderness in the right iliac fossa and gurgling is frequently obtained on pressure

but there is nothing characteristic in either of these. Retention of urine early in the attack may be suggestive.

The course of the fever in ordinary attacks is usually characteristic, as it is constant and rarely shows much variation. This is not always true and there may be a very irregular temperature curve, either early in the course or toward the end. If this be associated with chills the diagnosis may be difficult. If the diagnosis has not been made during the attack a temperature persistently below normal during convalescence from an illness with fever is always suggestive. The blood may not show any characteristic condition, although as a rule the number of leukocytes is below normal. A patient with fever and a leukocytosis certainly has not uncomplicated typhoid fever, so that, excluding a complication, an increase in the leukocytes suggests some other disease. In certain cases the differential count is of value, the special point being an increase in the mononuclear elements, especially of the larger forms, and a decrease in the polymorphonuclears and eosinophiles.

There are certain occurrences during the course of a doubtful fever which are important aids. Among these is the sudden appearance of deafness without any purulent process and the complaint of tender toes. The occurrence of hemorrhage or of perforation of the intestine is of course characteristic, while the onset of a phlebitis may clear up a doubtful attack. There are certain things which speak against typhoid fever such as herpes, coryza, and conjunctivitis. Sweating during the disease is rare, although it may occur at the onset, with certain complications, or during convalescence. Jaundice is rare, apart from gall-bladder conditions.

The special methods of diagnosis are dependent upon the demonstration of the typhoid bacillus or obtaining a specific reaction.

1. **Isolation of Typhoid Bacilli from the Blood.**—This is comparatively easy of application, does not give the patient much discomfort, and often gives valuable results. It is particularly useful early in the attack and for the diagnosis of cases with fever and perhaps no other positive sign. The bacilli are most frequently found in the blood early in the attack, perhaps before the usual signs of the disease, but later in the course they are not found so frequently and a negative result should not be given too much weight after some weeks of fever.

2. **Isolation of Typhoid Bacilli from the Stools.**—This involves more difficulty than the obtaining of bacilli in blood cultures but is usually possible. Cultures should be made immediately after the stool is passed.

3. **Isolation of Typhoid Bacilli from the Urine.**—The finding of actively motile bacilli in a specimen of urine recently passed is always suspicious. Cultures should be taken with great care and in identifying the organism the frequent occurrence of the colon bacillus must be remembered. Typhoid bacilli rarely occur in the urine before the end of the third week, so that this is not an aid in early diagnosis.

4. **Isolation of Typhoid Bacilli from the Spleen or Rose Spots.**—This is not suitable for practical purposes.

5. **Isolation of Typhoid Bacilli from the Spinal Fluid.**—This is of special value in patients admitted in delirium or stupor or with other severe

nervous manifestations. The procedure is simple, lumbar puncture being done in the ordinary way and cultures made from the fluid.

6. **The Ophthalmo-reaction.**[1]—A solution of one-third to one-half of a milligram of "typhoprotein" in a drop of water is instilled into the conjunctival sac. The best results are obtained from protein obtained from numerous different strains of bacilli. The characteristic reaction appears in one to five hours, reaches its maximum in about six hours and usually persists for twenty-four hours. There is a deep purple congestion of the palpebral conjunctiva of the lower lid and of the caruncle. The reaction is given most often during the acute stage and often before the Widal reaction.

7. **The Agglutination Phenomenon.**—Through the action of the bacteria on the tissues, soluble bodies known as agglutinins are produced in the blood, which when sufficiently concentrated have the property of clumping and rendering non-motile the specific organism whose activity gave rise to their production. To the agglutination phenomenon in typhoid fever the name of Gruber-Widal reaction is given. The technical details can be found in works on laboratory methods and diagnosis.

Diagnostic Value.—While the Widal reaction is almost always present at some period in typhoid fever, its appearance may be long delayed and it is rarely found before the seventh or eighth day. The persistence of the reaction is very variable, being from a few weeks to many years. Some instances of long persistence have been attributed to the presence of typhoid bacilli in the gall-bladder or in the urinary bladder. The agglutination of *B. typhosus* by normal sera at the standard dilution of 1 to 50 in one hour is so rare as to be of little importance in diagnosis.

The question of associated agglutination, in which a serum agglutinates two or more closely related organisms, is of little practical importance. As a general rule, if the agglutination test is done with a high dilution and a reaction within a limited time demanded (1 to 50 in one hour) we may expect to have reasonably specific results. If there be an infection with organisms of the paratyphoid group a positive diagnosis should not be made from the serum test alone but by means of blood cultures, as the possibility of the presence of associated agglutinins has to be kept in mind. A bacillus agglutinated by the patient's serum is not necessarily the causative agent of the disease, but this is strong presumptive evidence that it is.

In practical work the Widal reaction has a varying value. In one patient a positive result may give a diagnosis which otherwise might never have been made, while in another patient with undoubted signs of typhoid fever it may not be given until long after the temperature becomes normal. In a large series the number of positive results is high and should be over 95 per cent. The importance of testing the blood during convalescence must be remembered, as in several of this series reaction was given only on the day of discharge. In others it may be obtained only in a relapse. In comparing the results of different observers it is necessary to consider the technique as regards dilution, time, etc.

[1] See Austrian, *Johns Hopkins Hosp. Bull.*, 1912, xxiii, 1.

It seems fair to consider that the Widal reaction is of great value when a positive result is given and that, with proper technique, this justifies the diagnosis of typhoid fever, a previous attack being excluded. But to a negative result no great importance should be given, as shown by the number of reactions given for the first time late on in the disease. There is a group of results which may be termed "suggestive," in which, while a positive diagnosis is not given, there is some clumping and loss of motility. It is better not to admit such a division to our records, results being put down as "positive" or "negative," but it is impossible not to be somewhat influenced by these partial reactions. Such a finding is an indication to repeat the test in a few days. The persistence of the agglutinating power of the blood serum long after an attack of typhoid fever may be a cause of difficulty, especially if there be no history of the disease. We are hardly in a position to say to what extent mild attacks of the disease—perhaps not recognized—may be responsible for a reaction being given some time after.

Diagnosis from Other Diseases.—In some instances the diagnosis is entirely in doubt; we know that the patient has fever but are quite uncertain as to the cause. In other cases the patient with typhoid fever is regarded as having some other disease, or *vice versa*.

1. Tuberculosis.—The form which gives the greatest difficulty is acute miliary tuberculosis and considering the small number of cases of this disease it is probable that the mistake is relatively often made. Miliary tuberculosis is more often thought to be typhoid fever than the contrary. Both diseases may present the same general features without any definite local manifestations. The points which are of special value are as follows: The general appearance of the patient may be of assistance. In tuberculosis there is often a suggestive picture presented by the diffuse cyanosis, which is different from that seen in typhoid fever, associated with an increased respiration rate, although the bronchitis of typhoid fever may be so severe as to increase the respiration-rate and cause cyanosis. The temperature curve is often more irregular in tuberculosis and there may be considerable variation in a two-hour chart. The pulmonary signs are usually more marked in tuberculosis; an acute pulmonary emphysema, sometimes local and especially at the anterior border, is very suggestive of miliary tuberculosis. The pulse may assist, as in tuberculosis it is usually more rapid than in typhoid fever and is rarely dicrotic. A hyperemic rash, usually of a papular character, or petechiæ, especially about the wrists, may occur in tuberculosis. These might be mistaken for typhoid roseola. The abdominal condition is of comparatively little aid, for the spleen may be enlarged and diarrhœa or distension occur in both. Hemorrhage from the bowels rarely occurs in tuberculosis. The blood count may be of assistance, as leukocytosis may occur in tuberculosis, but even with a low leukocyte count the increase in the large mononuclears is not found as in typhoid fever. The examination of the eye-grounds may show tubercles of the choroid, although this is very rare. A lumbar puncture should always be done, as tubercle or typhoid bacilli may be found in the fluid.

Tuberculous Peritonitis.—This has not uncommonly been a source of error and the patients are usually thought to have typhoid fever, a mistake more likely to occur if the onset has been comparatively sudden. There is also a variety occurring with more or less continuous fever, abdominal tenderness and some distension, without any palpable tumor, which may give difficulty. The absence of signs of typhoid fever and observation for a few days should prevent error, which is probable only if the patient has not been seen from the onset or a correct history cannot be obtained.

2. Malarial Fever.—In the majority of cases with careful examination the diagnosis is not difficult. There are certain points to be kept in mind: (1) There is no such disease as "typhomalaria" or malarial typhoid." Typhoid fever and malarial fever are associated rarely but there is no third hybrid disease. (2) Any continued fever which resists quinine, properly given in ordinary doses for five days, is not malarial fever. (3) Careful examination of the blood should be made in every doubtful case of continued fever. The type of malarial fever which gives rise to difficulty is the estivo-autumnal, as in this chills may be absent, remissions of the fever very slight and the general appearance like that of typhoid fever. The intracellular organisms of this variety of malarial fever may be found with difficulty and in doubtful cases the blood should be examined every hour or two, because parasites may be present in the circulating blood only for a short period each day.

3. Typhus Fever.—The recognition of typhus fever may be exceedingly difficult, especially in the mild form described by Brill. The onset is of importance, for in typhus fever this is usually sudden and the temperature rises to 104° or 105° F. within two or three days, which is unusual in typhoid fever. The general features are usually much more severe early in the attack of typhus fever; thus delirium may appear in the first two days and coma be present by the beginning of the second week. The rash of typhus fever appears earlier than that of typhoid and the lesions attain their full development within one to three days. In typhus fever the rash is usually uniform over the trunk and extremities, especially over the forearms and legs, while the dorsum of the hands and feet is also frequently involved. The total duration of the fever in typhus is rarely longer than two weeks and it usually terminates rapidly.

4. Septicemia.—This may cause great difficulty, especially if it be of the cryptogenetic type without any localizing symptoms. There is often a leukocytosis and the differential count shows an increase in the polymorphonuclears. It is in such conditions that blood cultures are of special value. There is one group of these cases to which special reference should be made, namely, those occurring after labor or abortion. Pregnant women who have typhoid fever are subject to abortion or premature delivery and the exact diagnosis may be difficult. The leukocyte count and the result of the blood cultures are of great assistance. Typhoid fever may appear shortly after delivery and the diagnosis lie between it and puerperal septicemia. Gonorrhœal septicemia should be suggested by the local infection, the results of blood cultures, and endo-

carditis, if it be present. Certain cases of pyemia and pelvic abscess may give difficulty, especially if they occur without chills or sweats. Irregularity in the temperature curve and early rapidity of the pulse rate are against typhoid fever.

5. Endocarditis.—This may frequently cause confusion, especially if it be of the ulcerative type, and offers many points of similarity to septicemia and pyemia. The diagnosis may be especially difficult if the patient comes under observation late on in the attack. If he has been seen from the beginning the frequently abrupt onset, the irregular temperature curve, and the cardiac condition are all of value. The embolic lesions in endocarditis, the leukocyte count, and the results of blood cultures are important.

6. Influenza.—We may have much the same general early symptoms, and the frequent enlargement of the spleen with influenza is puzzling. Coryza at the beginning of the illness is strongly in favor of influenza and the bronchial symptoms with it are perhaps more likely to occur at an earlier stage. Observation for a few days should prevent influenza being regarded as typhoid fever, but it is not unlikely that many mild attacks of typhoid fever are regarded as influenza.

7. Febricula.—This is a common source of error in the distinction from mild attacks of typhoid fever. In some instances it is only the onset of a relapse that makes the diagnosis certain, as the general features may be almost the same. Enlargement of the spleen is quite common in febricula. One point of value may be the fact that with the return of the temperature to normal the patient with febricula often feels practically well. While this may occur in typhoid fever, as a rule even after mild attacks the patient's condition shows much more effect from the illness. The Widal reaction is of great aid.

8. Intoxications.—There are a number of toxic conditions which we frequently interpret as due to ptomain poisoning which may give difficulty in diagnosis. The organism often concerned in meat poisoning is nearly related to the paratyphoid group and the general features may be much like those of typhoid fever.

9. Osteomyelitis.—In children this has been mistaken for typhoid fever. Leukocytosis and the result of careful examination, especially in the region of the epiphysis, should aid.

10. The Acute Exanthemata.—Some of these may give difficulty, especially at the onset and in the absence of an epidemic. Measles, scarlet fever, and variola are the most likely to cause confusion. The early erythema sometimes seen in typhoid fever may suggest measles or scarlet fever. As a rule observation for two or three days will render the diagnosis clear.

11. Trichinosis.—Until 1860 this was usually regarded as typhoid fever and is probably often taken for it yet. This disease is probably more common than we suppose and in the great majority of cases is not recognized. In trichinosis the history of eating improperly cooked pork, the pain and tenderness in the muscles, and the œdema, especially of the face, are always suggestive. Rose spots and an enlarged spleen may be present in trichinosis but the spots do not come out in successive

crops. The blood examination, showing a leukocytosis with an increased number of eosinophiles, should at once attract attention.

12. Syphilis.—The secondary stage with fever, marked general symptoms and an enlarged spleen has been mistaken for typhoid fever, but careful examination and observation should make the diagnosis clear.

13. Miscellaneous Diseases.—Anthrax and acute glanders without local lesions may occasionally cause difficulty. Relapsing fever in certain localities has been taken for typhoid fever, but the course of this disease and the result of blood examinations should prevent any great difficulty in its recognition. Cerebrospinal fever may cause confusion; the results of lumbar puncture are the greatest aid. Abdominal actinomycosis may simulate typhoid fever. There are a variety of diseases which may cause difficulty, especially such as are associated with fever and more or less stupor. Thus catarrhal jaundice may give difficulty for some days, and also uremic conditions with fever.

14. Malignant Disease.—In certain instances in which this occurs with continued fever, general malaise, and no local symptoms or signs, the mistake may easily be made, usually of regarding malignant disease as typhoid fever. It is especially likely to occur when the new growth is situated in the liver.

In the group just considered the common tendency is to consider another disease to be typhoid fever. There now come a number of conditions in which the difficulty is due to an attack of typhoid fever beginning with marked symptoms in one organ or showing these during the course. Attention being directed to the organ especially involved, the other signs may be overlooked, and a definite although erroneous diagnosis having once been made, it is not easy to see the features which suggest something else. The diagnosis is true so far as it goes but it is not the whole truth.

15. Conditions of the Nervous System.—These are frequently a source of difficulty and it is important to remember that meningeal features in typhoid fever may be very marked. A careful search to find tuberculous lesions elsewhere in the body or conditions of the ears and nasopharynx is exceedingly important, but by far the most essential aid is lumbar puncture, which should be done as a routine in every patient coming in with meningeal symptoms. As a rule this will give the diagnosis at once in the epidemic, purulent, and tuberculous form of meningitis. In typhoid fever with meningeal symptoms we may find typhoid bacilli in the spinal fluid and so make the diagnosis. Kernig's sign may occur in typhoid fever without any meningeal involvement.

16. Pulmonary Conditions.—These are exceedingly important, by no means uncommon, and may be especially misleading at the outset. The initial bronchitis may attract the chief attention, but as a rule the increasing, constant fever soon suggests something more. By far the greatest difficulty is found with patients in whom the onset is with an acute lobar pneumonia. It may be only after a week that the persistence of the fever suggests some additional condition and careful examination may show rose spots. It may be impossible to avoid this error; the patient *has* acute lobar pneumonia and there may be no signs of

typhoid fever until the expiration of perhaps a week. The pneumonia coming on in the course rarely gives rise to difficulty unless the patient be seen for the first time after it has developed. An atypical form of pneumonia may be present at the onset. This may cause difficulty, particularly if the general symptoms are not severe.

Pleurisy.—The attacks beginning with an acute pleurisy may cause error. The diagnosis of pleurisy is correct so far as it goes but there is something behind it. If there be an effusion, routine cultures may give the diagnosis but if these be negative it may be difficult to recognize the condition at the onset.

17. Abdominal Conditions.—This is a most important group, as in the first place the ordinary abdominal features of typhoid fever may give difficulty and, secondly, the occurrence of abdominal complications before the patient is seen for the first time may be very confusing. Among those of the first group, gastro-enteritis may be suggested on account of severe diarrhœa, but perhaps the most common mistake is to regard the condition as appendicitis. Abdominal pain is comparatively common in typhoid fever, and if it is referred to the right iliac fossa and some tenderness is found, appendicitis is naturally suspected. Muscle spasm is rarely present in these cases of pain in typhoid fever. The leukocyte count is most helpful, for a normal or diminished number of leukocytes speaks strongly against an acute appendicitis, except in fulminant cases, which are rarely likely to be taken for typhoid fever. The caution may be repeated that under no circumstances should opium be given to a patient with a doubtful abdominal condition.

The occurrence of abdominal complications before the patient is seen may render the diagnosis difficult. Thus in one year three patients of this series were admitted with general peritonitis due to perforation of the intestine. In the absence of rose spots and with a doubtful history it may be almost impossible to make a diagnosis. Fortunately this is not of any great importance as regards treatment, the indications for this being those of the acute abdominal condition.

18. Renal Conditions.—These may cause much difficulty, as the attack may begin with symptoms suggestive of acute nephritis. The ordinary febrile albuminuria is not likely to cause confusion.

It may be said of diagnosis that no rules can be set down which apply to all cases. It is well to recognize the fact that diagnosis must often wait for several days' observation. In other instances only an autopsy or some incident during convalescence may make it clear. The more often bacteriological methods are used, the more alert we are to the possibility of mistake, the more care we take in frequent thorough examinations with open minds, the fewer errors will be made.

Prognosis.—There can be no certainty of the outcome or duration of an attack of typhoid fever and it is never safe to give an absolutely favorable prognosis. The patient with every symptom favorable may become seriously ill or have a severe complication without warning, while on the other hand in no disease do we see so many patients recover who have been desperately ill. Many factors have to be taken into consideration, but a word should be given to the care which the patient receives. Hard

work, stimulated by a spirit which never gives up while there is life, may pull a patient through a desperate attack. This is especially true of those with severe toxemia, who may owe their recovery directly to the perseverance of the physician and the care of the nurse. In many regards the outlook is better when the patient is treated in a hospital, for there are so many advantages, the better facilities, the constant nursing—possible only in few houses—and the more rapid dealing with emergencies. The treatment has some influence and those who use baths are undoubtedly justified in regarding the outlook as more favorable than under any other method. The stage of the disease at which the patient comes under treatment is an important matter, the earlier he is put to bed as a rule the better the prognosis. In patients who have fought the disease, the prognosis should always be very guarded.

There are many factors by which we may estimate the outlook in typhoid fever but it is a disease in which perhaps more than any other we are unable to tell what a day may bring forth. Of the conditions which cause death, we can estimate the danger with some degree of certainty in the most frequent, namely, toxemia. While it is impossible to say that toxic symptoms may not become more marked later in the attack, yet as a rule the danger of this is slight after the third week, especially under the bath treatment. The response to treatment with hydrotherapy for a few days is a great aid in the prognosis. Sudden death without any warning symptoms may occur during the height of the disease or in convalescence. As regards another factor—the complications—we cannot speak with any certainty, for hemorrhage or perforation may occur without any warning and the outlook be changed in an hour. We have large bodies of statistics of the death-rate with various complications but these may be of little help in estimating the chances for a given patient.

Epidemics vary remarkably and in some large ones the death-rate has been exceedingly low. Great variation in the mortality may be true of a certain locality or the same clinic from year to year. There may be much difference in the severity of the disease at various periods of the year or at different times in an epidemic. The early cases in the annual typhoid season are often more severe than those coming in after the epidemic begins to diminish. Dr. B. F. Royer has drawn my attention to the results of a study of the morbidity and mortality returns of Pennsylvania for seven years. These show that when the morbidity is highest the mortality is least, and *vice versa*. Thus the month of April, with 6027 cases for the period studied, has a death-rate of 20.6 per cent. and September with 14,345 cases a death-rate of 12.8 per cent. The number of deaths in each month does not show a very great variation, while, of course, the total number of cases varies greatly.

Race. — The death-rate among the colored patients is just double that of the whites. The diminished resistance of the colored race is important but the lack of care before admission is also a strong factor.

Sex.—There seems little difference between the two sexes, although in males there is more tendency to keep about after the onset and

alcoholism is another factor which renders their death-rate higher. In women the effect of pregnancy has to be remembered.

Age.—This is of much more importance. Up to the age of two years the risk is great; from two to fifteen years is the most favorable period and the mortality is low. As a rule from about fifteen up to twenty-five is a more favorable period than from twenty-five to forty years. After forty the danger increases with every year and over the age of fifty the death-rate is high.

Occupation and Position in Life.—These influence the mortality principally as they affect the chances of receiving treatment early in the attack. The outlook is better among those who are more likely to be taken in hand early. The group of patients who recive practically no care during the early part of the disease, such as men in lumber camps and construction gangs, tramps, etc., usually has a high mortality.

General Conditions.—There seems little doubt that newcomers to any locality who contract the disease are apt to have it in a severe form. As regards constitution, the fat generally give more anxiety than the lean patients, as the infection often seems to be more severe and their resistance less marked. Alcoholics and patients with marked anemia as a rule have a high death rate. The coexistence of chronic disease is unfavorable but an exception should be made of cardiac and vascular disease. Patients with arteriosclerosis or well-compensated cardiac disease seem to go through an attack of typhoid fever without any additional risk. Chronic tuberculosis does not seem to add to the danger.

Special Features.—*Toxemia.*—This is an important matter and its degree must always be considered. Delirium, coma, and tremor are always of grave omen, especially if they appear early. Of the various types, that characterized by low muttering delirium associated with tremor is perhaps the most serious. The amount of delirium or stupor, the tremor, subsultus, and other disturbances must all be taken into consideration. If the patients are being treated by baths, the effect of these on the symptoms is a great aid in giving a prognosis. The estimation of the danger of toxemia is also influenced by the amount of urine voided, for if the patient is taking large quantities of water and passing urine freely the outlook is more favorable. When there is difficulty in getting the patient to take water by mouth the prognosis is grave, although the giving of water by the bowel or by subcutaneous infusion may keep up the amount of urine. There are features which may be secondary to the condition of the nervous system or due to the local effect on various organs. Thus meteorism may be an indication of profound toxemia but it also has an important effect on account of the local condition in the intestine.

The early psychoses are of grave significance as regards life but those later in the attack and during convalescence do not materially alter the prognosis. As regards recovery from the mental condition the family and previous history are important. In the late psychoses, associated with anemia and exhaustion, the outlook is good.

In the circulation, the condition of the pulse is important and an increased rate is always serious. It may be said that every increase

above 120, which is more than temporary, adds to the risk. The blood pressure is of some assistance in the recognition of a failing circulation and a steadily falling pressure with severe toxemia is a grave sign. The condition of the heart is important and especially the character of the first sound, for if this becomes feeble or inaudible the outlook is always more serious as also if gallop rhythm or embryocardia is present. Marked cyanosis does not seem to be of any untoward significance.

Bronchitis rarely had any influence on the course. The ordinary lobar pneumonia may be the cause of death either early in the attack or later on, when it is probably of even graver significance. Bronchopneumonia is a very dangerous complication, especially in patients over forty years of age, and few recover from it. Hypostatic pneumonia is serious more on account of the conditions which have favored its occurrence than for any other reason. Pleurisy, either with or without effusion, adds somewhat to the danger. The complications in the larynx and epiglottis are serious, especially in patients severely ill, and there is always the danger of œdema of the glottis or bronchopneumonia.

Of the intestinal conditions, meteorism is always serious and should be regarded more as an evidence of the degree of toxemia than of any local condition. The result of treatment is an important aid in estimating its gravity. Diarrhœa is always a grave symptom, because it usually means either severe toxemia or a marked grade of ulceration, especially in the colon. Yet, as the older writers pointed out, in a patient with severe symptoms, the onset of a sharp attack of diarrhœa may prove beneficial. Hemorrhage is always more or less serious, yet when the figures are carefully examined, it is surprising to find how many of the patients recover. Of the 137 fatal cases in this series only 12 died apparently directly as a result of hemorrhage. Perforation under ordinary circumstances is rarely recovered from, for the proved cases of recovery from perforation without operation are very few. The outlook with operation depends on several factors, perhaps the most important being the time at which it is done after perforation has occurred. There is no question that the sooner the operation the better the chance for recovery. The extent of the peritonitis and the organism present are important, as with a general streptococcus peritonitis the outlook is always extremely grave, while with other organisms it is decidedly more favorable. The condition of the bowel is significant, as in some the whole lower part of the ileum and the cecum is almost necrotic, so that it may be impossible to make the stitches hold. The general condition and the degree of toxemia must also be taken into consideration, as a certain number of the patients operated on for perforation die subsequently of toxemia. Any other complication, such as pneumonia, after the operation, adds greatly to the danger. The death rate from perforation varies in different years and one hospital may have several successive cases of recovery.

The simple febrile albuminuria is not serious. With acute nephritis or the condition of so-called "nephrotyphoid" the prognosis is always more serious. The occurrence of typhoid bacilli in the urine and cystitis are not apparently of any special danger to the patient.

Phlebitis, while distressing, is rarely a cause of death. There are a few instances of detachment of a portion of the thrombus with resulting pulmonary embolism. As regards the outlook for the local circulatory conditions, a very cautious opinion should be expressed, as many of the patients are left with more or less permanent disability, and it is well to warn them of this at the onset of the thrombosis. The various glandular conditions as a rule are not serious and have little effect on the course with the exception of parotitis. It is always a grave matter and suggests a cautious prognosis. The occurrence of angina with cellulitis of the neck is rarely recovered from.

It is important to note the way in which the patient takes his nourishment and especially the amount of water. In general terms the degree of fever is not of great importance. Of course hyperpyrexia is serious, but high fever is not necessarily a serious condition. We see this markedly shown in the case of young adults who come in with high fever but no severe toxic symptoms; such as a rule do well and often run a comparatively rapid course to recovery.

Sudden Death.—In the memory of everyone who has treated many cases of typhoid fever there must stand out instances of a sudden termination without warning. These impress one so strongly that their frequency has perhaps been overestimated. There were 4 among 137 fatal cases in this series. It appears to be more common in men than in women and as a rule it is more common late on in the attack. The most frequent cause is probably myocardial degeneration, with which sudden dilatation or delirium cordis occurs. In certain instances embolism and thrombosis, either of the cerebral or of the pulmonary vessels, may be the explanation. A profuse intestinal hemorrhage may lead to a sudden termination.

Prophylaxis.—This is the most important part of the problem of typhoid fever and in the past too little attention has been paid to it, for while we have been willing to give every attention to the patient with the disease we have failed to carry out adequate preventive measures. We talk of infected water and milk as if they were the cause of the disease, forgetting that behind them lies the actual source. Typhoid bacilli do not naturally inhabit water or milk; they may exist in it for a time and even multiply, but their natural dwelling place is man and these are only carriers from one host to the next. The lesson is easy to learn but hard to carry into practice. Let us make sure that every typhoid bacillus is killed immediately on leaving every host and the disease is at an end. But there are difficulties in the way. Many of the attacks are so mild that the diagnosis is never made and these are unrecognized sources of danger. The country is so infected that it seems almost hopeless to begin the struggle and this applies with greater force to rural than to city communities. Yet every thorough measure of prophylaxis count, and when we consider how easy it might have been to prevent many epidemics had the proper care been exercised with the first case, there is much to encourage us. We cannot tell how many cases of infection may be prevented by thorough disinfectant measures with one patient.

If even the recognized cases are properly handled, that reduces the number of the subsequent unrecognized ones.

The subject may be considered under three heads: (I) general measures which are for the protection of the community; (II) special measures in connection with the patient; (III) preventive inoculation.

I. **General Measures.** — These are of wide application and belong rather to the domain of sanitary science. The problem is that of the supply of pure food and water. With the present prevalence of the disease there is practically no community in this country free from a certain degree of danger and the water-supply is everywhere a most important element. An important feature is the careful inspection and regulation of the area from which the water is derived. This is more or less uncertain at the best, as it is impossible to inspect a wide area and there may be mild cases of typhoid fever which are not recognized. The next point is the care of the water after it is collected, which means filtration and chlorination if the water is not pure. While in cities the obtaining of a pure water supply is comparatively easy, or should be, it is in rural communities and in country districts that the greatest difficulty comes. Here the prevention of infection from a given patient is all the more important. In fact, as conditions are today, it must be the only hope of stamping out the disease, for in a village or on a farm it may be quite impossible to change the water-supply. In all localities in which the water is not undoubtedly free of typhoid bacilli, or while the disease occurs, it is important to have the water boiled, but even when this is done there are many sources of danger, for infected water may be used to clean the cooking utensils, to wash vegetables, and for personal cleanliness.

As regards food the difficulties are perhaps even greater, for the sources of supply are so many and food must pass through such various hands that control is almost impossible. Undoubtedly the most likely food to carry infection is milk, which may be infected accidentally or water may have been added to the milk. In cities some of the distributing points are responsible, as small stores may supply milk to a neighborhood and it may easily be infected in such places. The control of this must be in the hands of the local sanitary authorities. Meats are very rarely the means of carrying infection, except at times the paratyphoid organism, but there can be no doubt that under certain circumstances oysters may do so. The danger nearly always comes from keeping them in infected water. Vegetables may also be the cause of infection.

It is evident that as regards the danger from the above sources the ordinary individual can do little to lessen it. He may see that his drinking water is boiled and that the greatest possible care is taken in the preparation of his food, but he cannot control the matter absolutely. How much more important, therefore, to prevent the necessity by killing the bacilli at the source. During the time of an epidemic every care should be taken to boil both water and milk before using them and all possible sources of infection through either of these should be watched and guarded against. Ice-cream may carry the bacilli past most of the ordinary defences.

The control of the Board of Health should be firm and thorough. Notification ought to be insisted upon and heavy penalities provided for any failure to report all cases with continued fever, whether diagnosed typhoid fever or not. The relation in the health reports of many cities between the number of cases of typhoid fever and the deaths suggests that perhaps only half of the cases are ever reported. The organization of rural hygiene would go a long way toward the solution of the control of typhoid fever. If every State had a staff of men who could be sent to an infected district and take control of the situation, we would see a diminished death-rate. There is no reason why this should not be done as carefully as if the patient had plague or cholera.

In armies or when large bodies of men are collected together, as in construction or mining camps, special precautions have to be taken. In addition to care in securing a supply of pure food and water there has to be special supervision of the means of disposal of the excreta. In permanent camps this is probably best done by the use of iron troughs which contain milk of lime or crude carbolic acid solution. Overcrowding should be prevented, army camp sites changed frequently and not used a second time. Every care should be taken to detect the first cases and all men with suspicious symptoms should be isolated at once. Endeavor should be made to keep flies out of the mess tents.

II. **Special Measures in Connection with the Patient.**—It is to these especially that we must look if the disease is to be stamped out. This point has been repeated over and over again, but until the profession realizes its importance and what is more, carries it into practice, the prevention of typhoid fever is more or less hopeless. Let any man compare his attitude toward a patient with typhoid fever and toward one with plague, cholera, or smallpox and we have the explanation of many of the difficulties.

1. Isolation.—How thoroughly should we isolate the patient with typhoid fever? In the hospitals of the United States, patients with typhoid fever as a rule are treated in the general medical wards, while in Great Britain they are usually removed to one of the fever hospitals. There is a certain risk in having these patients in the general wards and our duty to attend thoroughly to disinfection is all the greater. But there are advantages in having the patients in a general hospital, for students have an opportunity of studying the disease and certain of the complications, perforation especially, can be handled with more chance of recovery. Yet all hospital records show that there is some danger. When the patient is being treated in a private house it is best to carry out rigid isolation. The room should be prepared as for one of the more infectious diseases, all unnecessary furniture removed, and the other members of the family not allowed in the room. It is well to have separate dishes which do not go down into the general kitchen.

2. Disinfection.—Special attention should be given to the disinfection of the stools, urine, sputum, vomitus, and clothing. In addition the bath water should be disinfected and precautions taken against flies. The patient should receive careful attention and after each movement of the bowels the anal and sacral regions should be cleansed with a

1 to 40 solution of carbolic acid or a 1 to 1000 solution of bichloride of mercury. After micturition, if any urine has been spilled, the same should be done.

(*a*) *Stools.*—The most effective method is by heat, and special hoppers have been devised for this purpose for use in hospitals. The feces may be boiled in cauldrons in fever hospitals or during epidemics but in ordinary practice chemical disinfectants must be used, and the most effective of these are milk of lime and carbolic acid. Bichloride of mercury is not a reliable disinfectant for stools. Whichever is used two things must be insured—that a sufficient quantity of the solution is used, and allowed to act for a proper length of time. It is well to place a pint of the solution in the bed-pan before it is used and add an additional amount afterward. The solution and the feces should be thoroughly mixed and if there are solid masses these should be broken up. The mixture should be allowed to stand for three hours before being thrown out. It is well to keep the disinfecting solution in the bed-pan when it is not in use. (*i*) Milk of lime: This should be prepared from freshly burnt lime, air-slaked lime being useless, which is mixed with water in the proportion of 100 parts of lime to 60 of water. The lime should be allowed to soak up the water slowly and the resulting hydrate should be kept tightly sealed, as it readily takes up CO_2 and becomes useless. To prepare the milk of lime, one part by weight of the fresh dry hydrate is mixed with eight parts by weight of water; this solution should be prepared every day. It is not safe to depend on the commercial chloride of lime. Care should be taken to see that at least three times the volume of the feces is added. (*ii*) Carbolic acid: This should be used in a strength of 1 to 20 and at least twice the volume of feces added. As a rule the use of carbolic acid is to be preferred.

(*b*) *Urine.*—The necessity of constant care with this should be impressed on everyone who is handling a patient and especially when the nursing is done by members of the family. The nurses, attendants, and orderlies should be taught that the urine of every patient may contain typhoid bacilli and be a source of danger to themselves or to others. The prevention of the occurrence of the bacilli in the urine is an important matter and there seems little doubt of the value of the administration of hexamethylenamine in 10 to 15 grain doses three times a day. Of the disinfectant solutions the two most useful, as shown by Gwyn, are carbolic acid and bichloride of mercury. (*i*) Carbolic acid: For disinfection in one hour a third of the volume of urine of a 1 to 20 solution should be used. (*ii*) Bichloride of mercury: Of this one-fortieth of the volume of urine of a 1 to 1000 solution is necessary for disinfection in one hour. It is well to add sodium chloride, 0.5 to 1000, to the bichloride solution. The easiest method is to place the disinfectant solution in a large covered jar into which the urine is poured; this can be emptied every day. The disinfectant solution should always be in excess and the mixture allowed to stand for at least two hours after the last urine is added before being thrown out. The urinal should be kept in disinfectant solution when not in use.

The urine should be disinfected until the patient is convalescent,

unless bacilli are present, when disinfection should be continued for at least three weeks after these have disappeared. No patient should be discharged from observation without the certainty that his urine is free from typhoid bacilli.

(*c*) *Sputum and Vomitus.*—These rarely require disinfection because not often obtained. They should be disinfected by carbolic acid exactly as the urine. If the sputum is received in cloths these may be burned.

(*d*) *Clothing.*—The principal danger exists when clothing has been soiled but it is not always possible to detect this, as a few drops of urine on the linen may not be noticed, so that it is safe to disinfect it as a matter of routine. This is best done by soaking it in a 1 to 20 solution of carbolic acid for two hours and afterward all the linen should be boiled. The rubber sheets may be disinfected by soaking them in 1 to 20 carbolic acid solution. It is safe to sterilize the mattress by dry heat. Carpets and rugs are better taken up at the beginning of the illness, but if not, there is always the chance that they may have become infected and they should be sterilized by dry heat.

(*e*) *Room.*—Sunlight, fresh air and cleanliness are most important during the illness, but afterward the room should be disinfected by formalin.

(*f*) *Bath Water.*—This must be frequently infected either by small fecal particles or by urine. Chloride of lime has been found to be the most efficient disinfectant, one-half pound, acting for one hour, being enough for the ordinary tub. This should be used only from fresh tins and not after these have been open for two or three days.

(*g*) *Bed-pans and Urinals.*—These should be isolated and scalded after each disinfection of their contents. The enema syringes and rectal tubes should be isolated and boiled after using. The urinals, syringes, and tubes can be kept in one of the disinfectant solutions.

3. Flies.—Every endeavor should be made to keep these away from the patient. If possible the windows should be screened but if flies do get into the room every effort should be made to kill them. Netting may be put over the patient but it is difficult to keep this in place.

4. Attendants.—All those who are handling the patient should be especially careful to disinfect their hands whenever the patient has been touched. The hands should be thoroughly washed with hot water and soap and then disinfected in 1 to 1000 bichloride solution. Nurses should wear rubber aprons when they are giving the baths or sponging the patient. It is important for physicians and medical students to remember that great care should be taken in the examination of the urine. In a hospital the orderlies should be especially watched, for much of the handling of the patients is done by them and it requires constant care and vigilant oversight to make sure that the orderly who is attending typhoid fever patients carries out all the procedures. It is most important to see that he does not come in contact in any way with the food or water supply of the ward and he should not be allowed about the kitchen or permitted to carry any nourishment to the patients. In hospitals it should be the endeavor not to allow the nurse who is handling typhoid fever patients to have anything to do with the food

supply of other patients in the ward. If possible in private practice, the individual who is nursing the patient should have nothing to do with the preparation of the food of the rest of the family. If this be unavoidable the most careful precautions should be taken.

In hospitals and places where the drainage enters into a proper sewage system there is often difficulty in having disinfection thoroughly carried out, for it is felt that the bacilli are to be carried where there is no chance of their doing further harm. We are not sure of this in any place—oysters may be fattening close to the outlet of the sewer—and besides it is our duty to destroy every bacillus, no matter where it otherwise might go. In hospitals it is most essential for the proper training of the nurses that they carry out the methods very carefully, for if not compelled to do so when in training they are not likely to do it later among other surroundings.

III. **Antityphoid Inoculation.**—The practical application of vaccination as a means of prophylaxis is due largely to the work of A. E. Wright. The material used consists of a bouillon or agar culture of the *B. typhosus* which is sterilized by heating to 53° or 55° C. for ten to fifteen minutes. A number of different strains are mixed together and a small amount of tricresol or lysol is added. For the first inoculation an amount of the vaccine containing about 500,000,000 of bacteria is used and for the second and third injections 1,000,000,000, the inoculations being given at intervals of ten days. After the injection there is local redness and pain and frequently enlargement of the neighboring lymph glands. There are generally some constitutional symptoms, slight fever, malaise, and perhaps nausea and vomiting, but these usually pass off rapidly without any permanent ill effects. Those who have had typhoid fever usually have a more severe reaction. There is a great increase in both the bactericidal and agglutinating elements in the blood.

The value of this method has been thoroughly proved, especially in the American Army, in which the occurrence of typhoid fever has been reduced to a minimum. It has also been thoroughly tested as a means of protection for those who are attending patients with typhoid fever. There need be no hesitation on the part of the profession in advising its adoption by the public. It is useful for those who have to visit or live in typhoid infected localities for the idea, previously held, that for a short time after the inoculation there was a negative phase during which there might be a slightly increased susceptibility to infection, does not seem to be correct. While we are not able to speak as yet with certainty as to the duration of the protection it usually persists for two years and in some cases for a year longer.

Prophylaxis is best attained by killing the bacilli when they leave the patient. Let no one imagine that this is easy to do, for it involves much more labor and conscientious care than the majority of mankind are likely to give. It is in the supervision of this that power given to competent authorities should be so valuable.

Treatment.—The most important points in treatment are simplicity in the method, care in the nursing, constant watching and common-sense throughout. We cannot abort the disease, we have no specific treatment,

and the problem is to bring the patient through a severe infection. We should know our limitations and the dangers of misdirected zeal. Among one hundred patients with typhoid fever there is a large proportion who will recover with ordinary careful expectant treatment, a small number who will die despite all care, and an intermediate group the members of which recover or die, depending on our treatment. The decrease in the death rate comes from saving members of this intermediate group. The most frequent cause of death in toxemia, a condition which has to be kept in mind in every patient; a smaller number die from complications, and to save some of these the early recognition of the condition is necessary. To make a prompt diagnosis of perforation is as much our duty as to know how best to treat hemorrhage.

It cannot be repeated too often that there is no routine method of treatment. Nor is our duty only to the patient. It is more important to the community that there is no danger of infection to others than that a given patient should be brought safely through an attack. There is just as heavy a responsibility on us to see that the patient's urine and feces are disinfected thoroughly as to recognize a perforation early enough to give the best chance for recovery.

Can we cut short an attack of typhoid fever? There seems no proof that we can. Infection having occurred typhoid fever cannot be aborted any more than scarlet fever or measles. The course of the attack can be modified but more than this we cannot do. There are mild attacks in which the temperature may be normal within two weeks and the rose spots may appear after defervescence. If a favorite treatment has been used the course is attributed to this, but it is well to remember that such results occur without any drugs being given.

A point which frequently comes up for decision is the advisability of a patient travelling to his home or to a hospital some distance away. If there be no facilities for treatment or if the patient is seen at a very early stage a short journey may be permissible, but any long journey should be advised against strongly. Patients who have travelled are usually made much worse and the mortality among them is high.

There is a great difference of opinion as to the giving of a purge at the onset or early in the disease. Many who give no purgatives during the course advocate calomel at the onset, with the idea that the course is modified. The opinion of the writer is against the use of purgatives during the acute stage of the disease. It is interesting to note that in many of the patients who have diarrhœa early in the attack, this has followed the taking of purgatives. The less interference there is with the bowels the less trouble there will be from intestinal disturbances.

The ordinary treatment will be considered under the heads of (1) general considerations, (2) expectant treatment, (3) hydrotherapy, (4) treatment by drugs, and (5) serum treatment. The general management of the disease will be discussed and then the treatment of special conditions and complications.

1. **General Considerations.** — Care in the diet, good nursing and hydrotherapy are the most important measures. Drugs may be useful

for certain conditions but do not enter into the essential treatment. Care and nursing mean much and in no disease do we receive as much aid from an intelligent nurse. If possible the patient should be treated in a hospital. The advantages of this are many, for in few houses can a patient be handled as satisfactorily as in a hospital. The nursing can be done in a better way, the complications may be recognized and treated earlier and the requisite disinfection carried out more thoroughly. In country practice and in many places hospitals are not available and the best has then to be done in the house. In this event a large, airy room with good ventilation should be chosen. In summer he may be out of doors for part of the day if the house is so arranged that this is possible. A nurse should be in charge. If this is not possible and the nursing is to be done by the family or by unskilled attendants, careful *written* directions should be given as to the diet, sponging, and disinfection of the stools and urine. These should be specific in every particular and leave as little as possible to the discretion of the attendants. The quantity of nourishment and water to be given ought to be positively stated. Instruction should be given to watch carefully for the appearance of important symptoms, such as abdominal pain, and the conditions for which the physician is to be called at once, ought to be written down. Every detail should be considered, for the sum of minor points may mean much. Indefinite directions should be avoided. It is well to have a special chart kept so that exact knowledge is possible.

The patient should be put to bed at once, even if the fever is slight or if there is only a suspicion of typhoid fever. We are too apt to temporize and allow a patient with fever but uncertain diagnosis to go about for several days when he should be in bed. This is always a mistake and any fever in a doubtful case should be the sign for complete rest. The woven wire single bed with a mattress of medium hardness is best. A rubber sheet should be over the mattress, at any rate opposite the centre of the bed, and care should be taken to see that the sheets are smooth. Usually the patient is most comfortable with only one pillow and very light bedclothing. There are certain things to be carried out in every case. Absolute rest should be the rule from the beginning and the patient should not be allowed to get out of bed or do anything for himself which involves exertion. There may be some difficulty in the use of the bed-pan at first but it is usually possible to accustom the patient to its use and later it may be essential for him to use it, so that as a rule trouble is saved by insisting on its use from the beginning. More difficulty may be found with urination, many finding great difficulty in voiding while lying flat. Such a patient may be slightly raised or turned on one side, but it is well to be firm and insist on his not getting up, for as a rule this difficulty disappears in a few days. Occasionally retention may require the use of the catheter but this is to be avoided if possible, and hot applications to the hypogastrium or an enema of hot water are often effectual.

The matter of absolute rest involves the prohibition of visitors, and the fewer people that the patient sees the better. This may be difficult

in a private house and can be more easily arranged in a hospital. When patients are very dull, visitors do less harm but in any condition the fewer the better. There should not be any attempt to read to the patient nor should well-meant efforts to amuse him be allowed, for these only tire him to no purpose. Business matters should be strictly forbidden, although distress of mind may be saved by allowing a patient to make arrangements and give directions at the onset of the attack.

There should always be careful attention to the *mouth*. After each feeding the tongue and teeth should be cleaned and it is advisable to use a mouth wash. The following is a useful formula: carbolic acid (1 to 20 solution), glycerin, āā ℥j (30 cc.), boric acid (saturated solution) ℥viij (250 cc.). The proportions can be changed if desired and it is sometimes well to increase the amount of carbolic acid. Borax and glycerin is also a good combination, while glycerin alone may be freely applied to the tongue, teeth and lips. The nose should be watched and an alkaline spray used if the nostrils become obstructed.

Absolute cleanliness of body is essential. Special attention should be given to the back and it ought to be rubbed with alcohol several times a day. The dorsal, sacral, and anal regions need special care, and it is well to have the buttocks washed with a weak solution of carbolic acid (1 to 40) after each stool. A dry dusting powder should be freely used.

The stools should be carefully watched, and it is a good rule for the physician to see a stool at least every two or three days, and every day if there be diarrhœa. The presence of milk curds should be looked for, while every stool containing blood should be saved for inspection. Care must be taken, especially in the country, to prevent flies getting at the urine or stools. Constant attention must be given to the disposal of the excreta and specific instructions should be *written* out in every case, if printed directions are not available. The attendants ought to be warned of the danger of infection and the need of care.

Regarding the routine use of alcohol there does not seem any reason why it need be given in an ordinary attack and the great majority of patients go through the disease perfectly well without it.

Diet.—The general tendency of recent years has been to increase the amount of food given to the typhoid fever patient. The correctness of this is established, but discretion should always be used and the diet chosen for each patient. To nourish as much as possible in a long debilitating disease is important, but care is required to avoid doing harm by overfeeding. The patient should not be given more food than he can properly digest. There is no question of the value of carbohydrates in sparing the body proteins and they should be given in large amounts. As to the fats, as large amounts as are possible can be given with advantage. Excessive amounts of protein may do harm, and if given the effect should be carefully watched. The value in calories, which should be regarded as a fair average, may be put at 3000, but Shaffer and Coleman advise increasing this to 4000 to 5000 calories. Emphasis should be placed on the need of adapting the diet to the patient; no rule applies to everyone.

(*a*) *Milk.*[1]—This is the most valuable single food in the majority of cases and there are few patients who cannot take it in some form. The amount to be given must be settled for each patient, but a fair average is one and a half quarts (1500 cc., about 1000 calories) in twenty-four hours. It is sometimes well to dilute the milk with plain or lime water, or in some cases with an alkaline water, slightly effervescing if desired. Certain modifications can be used, such as boiled or peptonized milk, whey, buttermilk, malted milk, koumiss, or one of the fermented milks; the addition of some flavoring, such as vanilla, is sometimes an advantage. It is well to give some of these modifications if undigested curds are passed, or if there is diarrhœa or meteorism. Whey is often particularly useful in such cases. *Cream* is a useful addition, and may be given as such, added to the milk, given diluted with water, or in cocoa or coffee. It may be given at first in small amounts, 2 to 4 ounces a day, and gradually increased to larger amounts. Each ounce represents about 60 calories. Ice-cream is particularly useful for children. Care should always be taken to be sure that it is made from pure materials.

(*b*) *Eggs.*—The whole egg may be given either raw or lightly boiled. The average value of each egg may be put at 75 calories. One or two eggs each day may be given at first and the number increased to four or six. The white of the egg may be given as albumen water. The whites of two eggs are beaten up with a little water and strained; fruit juice, sugar, and water to 6 ounces are added. This makes a very palatable drink and may be given frequently. Considerable carbohydrate can be given in the form of sugar in this way.

(*c*) *Sugars.*—It is by these that we can most easily add to the amount of carbohydrate. Cane sugar can be given in drinks, such as lemonade, but lactose is more useful. This is well taken, and is given in various ways. At first 2 or 3 ounces per day can be given and this gradually increased two or three times or even more. It can be added to each feeding of milk or a solution made and added. Each ounce of lactose represents 125 calories. A tablespoonful represents about 38 calories. Lactose may also be added to albumen water, lemonade or ice-cream. Glucose can be given, but usually the patients soon tire of it.

(*d*) *Broths, Beef Extracts, etc.*—As a rule these are better left out of the typhoid fever dietary. If given they should be with the object of variety rather than giving nourishment. Bouillon and clear soups are the best form. Broths and beef tea are better not given, as they often cause intestinal disturbance. The various predigested protein foods are better avoided. They may be toxic, often cause diarrhœa, and are not without danger when it is difficult to get the patient to take other food. There is not the same objection to the prepared carbohydrate foods.

[1] It is important to be sure that the milk is pure. This applies not only to the presence of typhoid bacilli but of other organisms. Many digestive disturbances may be due to the milk, a point to which Edsall drew attention in reporting an instance in which the milk-supply of a hospital was responsible for much intestinal trouble among the typhoid patients. It is always important to examine the milk and its source very carefully, and if there be any doubt the milk should be boiled.

(*e*) *Other Liquids.*—Cocoa made with milk and to which lactose and cream are added is excellent if it agrees. Chocolate is less useful as it often causes nausea. Tea and coffee may be given with cream and sugar. Iced tea is often grateful and lactose may be added to it.

The above articles of diet may be given during the height of the disease. My own feeling is that during this period the majority of patients with severe attacks do not wish any more and have no desire for solid food. There are certain additional foods which may be given if warranted by the condition.

(*a*) *Carbohydrates and Fats.*—Milk or cream toast, crackers in milk, thin bread and butter, gruels, well-boiled cereals, mashed potato, well-boiled sago and tapioca can be given. To these fat may be added as cream or butter.

(*b*) *Protein.*—Gelatin can be given in any desired form. Junket, custard, and egg custard are usually allowable.

(*c*) *Fruits.*—Apple sauce and the inside of a baked apple are usually permissible. There is no objection to fruit juices, such as of the lemon, orange, and grape fruit.

In every case the condition of the patient and the effect of the diet must be considered. With diarrhœa or meteorism a decrease in diet to very simple foods is advisable. To nourish the patient as well as possible without causing disturbance should be our aim. It is possible to estimate very easily the food value of the nourishment which the patient is taking by keeping a food chart.

The question arises as to whether the patient should be waked for nourishment. The majority wake occasionally through the night and at these times it is well to give food. Patients with mild symptoms may be allowed to sleep for some hours but as a rule it is well to give nourishment—and especially water—at regular intervals. These may be every three hours during the night, but there is no general rule and this point must be governed by the conditions present. Great care should be taken in feeding patients who are dull and stupid to be sure that they are sufficiently aroused and able to swallow before food is given, as otherwise liquids may pass into the larynx and trachea.

Water.—With the question of feeding goes an equally important one —the giving of water. The need of large amounts of water is often forgotten and it is not sufficient to let the patient take water only when he desires it. There should be a constant endeavor to induce him to take larger and larger amounts and while awake he should take water at least every hour. It is a good practice to keep a supply at the bedside so that the patient can help himself if he is able and this may be done easily by a rubber tube. The giving of flavored drinks, such as lemonade, is of help in increasing the amount of water taken. Some patients will suck ice freely. There is no doubt that we can reduce the severity of an attack by giving large amounts of water, and this is especially important for the delirious and toxic patients, who should be constantly induced to take it. It is well to have a rule that the patient should take 3 liters (100 ounces) of water *per diem* as a minimum and much better 5 or 6 liters. To be certain that a typhoid fever patient is being

given enough water requires constant effort. If the patient be conscious and intelligent the importance of this can be explained to him and he is usually a willing assistant. Many patients learn that by drinking large amounts of water the fever is lower, they are more comfortable and not likely to have as many tubs. There seems no doubt that the patients who are under this washing-out treatment are likely to have milder attacks. It is internal hydrotherapy.

2. **Expectant Treatment.** — General care as noted above and the meeting of complications as they arise, describe this method. The disease is allowed to run its course with the hope that the outcome may be favorable. No special form of treatment is used, though as a rule some form of hydrotherapy is employed, either sponges or the wet packs.

3. **Hydrotherapy.** — In some form this enters into practically every method of treatment. With patients treated at home the use of sponges or packs may be the only method which can be carried out.

Sponges.—These may be given with the water at any temperature but as a rule cold or iced water is best. Alcohol sponges may be used in some cases. If sponges are given throughout the attack they are usually administered when the patient's temperature is 102.5° or over and as a rule every three hours. It is generally well to use a good deal of water in sponging and the duration should be twenty or thirty minutes. In some cases *vigorous* rubbing with ice is useful during the sponging. Special attention should always be given to the back and it is probably well to devote at least half the time to it. With patients who are very feeble and with very young or very old patients, sponges are often best. They are usually employed for patients with hemorrhage or phlebitis, when lifting into the tub might be harmful.

Packs.—These are useful if there be complications, for children and for delirious patients who cannot be given the tub baths conveniently. It is well to sprinkle the patients with cold water while they are in the pack and in severe cases one may use active friction. In excitable or delirious patients it is sometimes best to begin with the packs fairly warm and gradually reduce the temperature. While sponges and packs give comfort to the patient and undoubtedly are helpful, their effect is in no way to be compared to that which follows hydrotherapy in the form of baths, which almost seems to deserve the designation of being a specific treatment. The effects of the tub baths are quite distinct from those which follow sponges and packs. If begun early in the disease they usually have a marked influence on the course and may be said to be preventive as regards many of the dangerous complications.

Tub Baths.—With this form of treatment the mortality is lower than with any other, but if used it should be done from the onset and carried out systematically. It is well to begin the tubs as early as possible even if the symptoms be mild. We can never know how severe an attack may become, and if begun early the bath treatment lessens the likelihood of severe manifestations later in the disease, especially those due to profound toxemia. To use the baths only in severe attacks or to wait until the patient is desperately ill before beginning them, is fair neither to the method nor to the patient. The effects on the various

systems cannot be strictly limited, for through an improved state of the nervous system all the functions are improved, and this again may be largely due to the increased excretion of toxins.

(*a*) *Nervous System.*—This may be put first, for the nervous symptoms are to some extent an index of the toxemia. With the baths the severe symptoms usually improve rapidly; delirium lessens, muscular tremors diminish and the mental state clears. If begun early the severe toxic symptoms do not often occur. The old-time severe "typhoid state" is rarely seen in a clinic in which the bath treatment is systematically used.

(*b*) *Increased Excretion of Toxins.*—This occurs largely through the kidneys and is one of the most important results of the baths. The amount of urine and excretion of toxins are both increased, the result of this being seen especially in the state of the nervous system.

(*c*) *Circulation.*—There is a great stimulation of the vasomotor system. The heart rate usually falls and the pulse becomes smaller and harder; the soft, flabby pulse before the bath is in marked contrast with the firm pulse after it. There is usually a rise of blood pressure, which is on an average about equal to 15 mm. of Hg. The lymph circulation is probably also affected and through the improved lymph and blood circulation all the systems benefit.

(*d*) *Respiratory Tract.*—At the beginning of each bath the patient takes at least three or four very full breaths, expanding the lungs thoroughly and later breathes more deeply than normal. This diminishes the chance of passive congestion which is seen very rarely in clinics where this treatment is used. The initial bronchitis is usually greatly benefited.

(*e*) *Digestive Tract.*—The general absence of gastro-intestinal disturbances is due partly to the baths, but the simple diet and other care are also important. The improved condition of the mouth is marked.

(*f*) *Skin.*—The liability to bed-sores is much diminished, the frequent cleansing of the skin being a good prophylactic. Should boils occur, one tub should be used for that patient alone.

(*g*) *Reduction of Mortality.*—This is the main purpose and follows the improved conditions noted above. By the bath treatment systematically carried out probably five to seven patients are saved in every hundred. There are no more convincing figures than those published by Hare of Brisbane. From 1882 to 1886 in the Brisbane Hospital under the expectant treatment there were 1828 cases with 271 deaths (14.8 per cent.). From 1887 to 1896 under the bath treatment there were 1902 cases with 143 deaths (7.5 per cent.). The only change between the two periods was the use of the baths. Typhoid fever the world over has about the same mortality under the expectant treatment, and while this varies in different epidemics and localities, in any large series will be found to be about 15 per cent. Under the bath treatment a large series will show a saving of five to seven patients per hundred. Large figures have to be taken and the results of many hospitals combined. The mortality of a given hospital should not be taken alone, for let a hospital gain a reputation for success in handling the disease and it is apt to have patients sent in late in the attack who are in a dangerous condition.

(*h*) *Reduction of Temperature.*—Let it be clearly understood that, despite a common opinion, this is *not* the main object of the baths. During the height of the attack the baths may have but little influence on the fever, although markedly improving the general condition; later in the attack there may be drops of one to four degrees.

Objections to the Bath Treatment.—There are many urged against it. That it means much work to all concerned is not denied, but is this not a cheap price to pay for saving five to seven patients in every hundred? That they are cruel the writer does not believe, and this is said from observation of many patients and from personal experience. Much depends on the way in which they are given, and no man should carry out the bath treatment without instruction and experience. If many patients make complaint it means that the baths are not properly given. There will always be some complaint under any method, for an attack of typhoid fever is not a pleasant matter at the best, but with care complaints can be reduced to a minimum. The practice of beginning the baths only when the patient is very ill or as a last resort should be condemned. If used they should be begun early and used systematically. That they increase the frequency of complications is not proved, and the incidence of hemorrhage and perforation does not seem to be greater. Relapses may be slightly more frequent but more patients are saved to relapse. Attention should also be drawn to the fact that the giving of alcohol is not necessary with the bath treatment. A patient may need alcohol, but it is not because he is having tub baths. Many writers have the mistaken notion that alcohol has to be given after the bath. In reality alcohol tends to undo some of the desired effects of hydrotherapy.

Method of Tubbing.—The baths are given every three or four hours when the temperature is 102.5° F. or over. Even if the fever be persistently high the maximum number of tubs given in the twenty-four hours is seven, for there is usually a little time lost with each tub. The tubs are given for fifteen or twenty minutes. The temperature of the water varies from 70° to 85°; there is no routine and the temperature is chosen which does best for that patient. This is an important point to which attention is drawn. As a rule the lowest temperature (not below 70°) which the patient stands well should be chosen. The first bath is usually given at 85° and succeeding ones 5 degrees lower until the most suitable point is reached. No ice is used in the tubs, which should be noted as they are often spoken of as "ice baths." Much depends on the first bath, which is best given during the day and with the physician present and as a rule for not longer than ten or fifteen minutes. Should the patient be delirious, the first bath can be given at 70°, and in these cases cold applications to the head should be used.

A tub on rubber wheels which run without noise is the most suitable. It may be filled outside the ward and wheeled to the bedside, which seems better than having the patient's bed moved to the bathroom. It is well to add one pound of alum (previously dissolved in hot water). This keeps the skin in better condition and reduces the chance of boils and bed-sores. There are various methods in use to support the patient

in the tub. In some clinics a stretcher is used, the patient being placed on it and then lifted into the tub. This is useful for very heavy patients. Canvas strips 40 inches in length and with a width varying from 15 to 30 inches are very satisfactory. These are placed across the tub and held in position by clamps on its side which permit of easy alteration in the height of the canvas. The strips are arranged to support the patient at the proper depth and when he is in the tub they can be easily changed so as to make him as comfortable as possible. The head is supported by a rubber ring or pillow. The patient is prepared as follows: The bedclothing and gown are removed under a sheet and if he has been perspiring he should be rubbed dry. It is well to place a small amount of cotton in the ears. The patient is then lifted into the tub by two attendants; one slips an arm under the patient's head, which is supported in the bend of the elbow, and lifts him by the hands under the shoulders; the other attendant lifts the feet. When they are ready the patient is asked to hold himself stiffly and is then lifted into the tub. This involves only slight exertion and often less than there is in putting the patient on a stretcher. As soon as the patient is in the tub he should be made as comfortable as possible. The canvas strips should be so arranged that the water just covers the chest; with the head properly supported the ears ought to be out of the water. The canvas strips should support the body evenly. A compress wrung out of cold water is put on the forehead and changed occasionally. If nervous symptoms are marked it is well to apply cold affusions to the head frequently.

While the patient is in the tub he should be rubbed *constantly*. This is a most important part of the treatment. Brisk superficial rubbing with the flat hand is better than kneading of the muscles. Special attention must be given to the hands and feet, and it is better not to rub the abdomen. During the bath the state of the patient varies greatly; some are comfortable, others shiver and complain of the cold. There may be cyanosis and blueness but these need not cause any alarm. The patients who shiver greatly during the bath and after it often seem to do very well and it certainly is not a bad sign. It probably means an active vasomotor response. The patient should be removed from the tub if there be great distress, unusual cyanosis or collapse, all of which are rare. Vomiting, hemorrhage or complaint of abdominal pain are also indications for immediate removal.

The bed is prepared by putting a rubber sheet over it and on this an ordinary sheet. At the end of the time a fresh sheet is put over the patient in the tub, the wet sheet which has covered him is pulled down to the end of the tub and the patient is lifted out in the same way as he was put in. He is then wrapped in the sheets and covered with one or two blankets. As a rule there is a warm glow and the patient feels very comfortable. At the end of ten minutes he is taken out of the sheets, rubbed dry and the gown and bedclothing replaced. The "after-tub" temperature is taken twenty to thirty minutes after the bath. Nourishment or a hot drink may be given during the bath or as soon as the patient is taken out, but alcohol is *not required* as a routine after the bath. It should be given if the patient's general condition demands it and not

because he has had a bath. The patient usually falls asleep after the bath and feels more comfortable. If there is no reaction, which is rare, hot drinks should be given and hot bottles put around the patient.

It cannot be too strongly emphasized that if there be trouble with the baths there is some fault with the way in which they are being given. The use of water at the temperature best suited for the patient and careful attention to the details which mean so much for his comfort go far in preventing any trouble. There are modifications; the temperature of the water may be kept between 80° and 90° or the gradually cooled bath may be given.

The contraindications to the baths are severe abdominal pain, hemorrhage, any signs of peritonitis or perforation, cholecystitis, phlebitis or great prostration. Warm baths have been suggested for patients with acute nephritis. Patients admitted late in the disease with grave symptoms are not tubbed as a rule, although if they can take the baths, they are usually benefited. It is well to begin with baths at 85° for a period of ten minutes in such cases, and also with very young or old patients the same may be done or some other form of hydrotherapy used. Menstruation is not necessarily a contraindication, although it may be well to omit the baths for a day or two. Women patients who are pregnant take the baths perfectly well. Pneumonia and severe bronchitis are not regarded as contraindications, in fact they are usually improved by the baths.

In private practice one of the portable tubs which can be placed on the bed can be used. This can be filled by a hose and emptied by a siphon, but they not so satisfactory as the plunge bath.

It may be said again that the tubs should not be used in a routine way for every patient any more than any other form of treatment. Consideration has to be given to the individual and if this treatment be used it ought to be in the way which does best in that particular case. Thus some patients are tubbed only when the temperature reaches 103°, or if there be marked toxic symptoms, even with the temperature below 102.5° the baths are given regularly without reference to the fever. The indication for their use is the condition of the patient, and the temperature is usually a fair guide to this but may not be. In some cases the baths may be omitted during the night.

4. **Treatment by Drugs.** — There is no specific drug treatment. In many clinics hexamethylenamine is given as a routine with the object of decreasing the chance of bacilluria occurring and in the hope that there may be a diminished chance of cholecystitis. The usual dose is 30 to 40 grains (2 to 2.6 grams) a day. The urine should be carefully watched for hematuria and the drug discontinued if this or marked irritation occurs. Many practitioners give a fever mixture, quinine or dilute hydrochloric acid as a routine. There are two classes of drugs which should be specially considered.

(*a*) Antipyretic Drugs.—These have been given with the intention of reducing or keeping down the temperature, the coal-tar products being especially used, but the value of any of them is doubtful. The fever is only a symptom of the infection and to reduce it has no influence on

the essential processes of the disease. Then such drugs often do harm by their depressing action.

(*b*) Intestinal Antiseptics.—These have been used very extensively and many have been employed, such as salol, carbolic acid, chlorine water, β-naphthol, acetozone, etc. That they are of value is not proved and their use is based on a wrong idea of the nature of the infection. However, the majority of these drugs do no harm, which is more than can be said of the antipyretics.

5. **Serum Treatment.** — This is as yet in a more or less experimental stage, but we hope that the future will see the production of an effective serum. The work done has been along two lines, bactericidal and antitoxic, but there does not seem any proof of the production of any other than a bactericidal serum. A so-called antitoxic serum has been used in Paris by Chantemesse. A low mortality under its use is claimed, but its value has not been generally accepted. In the preparation of these serums—whatever be their value—different strains of the *B. typhosus* should be used. Both on theoretical and practical grounds little is to be expected from the use of bactericidal serums.

Vaccines.—The value of these cannot be regarded as established. Extensive experience is required before we can pronounce positively regarding this treatment.

Treatment of Special Conditions.—Toxemia.—When severe this may require special treatment. One of the greatest difficulties is to persuade the patients to take enough water and in this they should be encouraged in every way. If it be impossible to get them to take more than a small amount or if they refuse it altogether, salt solution may be given by the bowel, 250 to 400 cc. every six hours, a soft tube being used and the fluid given slowly. In serious cases, salt solution (750 to 1000 cc.) can be given by infusion once or twice *per diem*. In some patients the administration by the "drop method" is better. By these means we can keep up the amount of urine and favor the elimination of toxins. There may also be difficulty in getting these patients to take sufficient nourishment and in this case they may be fed through the stomach-tube, milk (150 cc.) well diluted or the whites of three or four eggs in water being given. Rectal feeding may be used but is rarely satisfactory. Alcohol is usually indicated in severe toxemia and is best given in the form of spirits, either whisky or brandy. Champagne may be used if it agrees better than the other forms of alcohol, but whatever is chosen, care should be taken that a reliable brand is used as adulterated liquor may do the patient more harm than good. The amount of whisky may be from 4 to 12 ounces in the twenty-four hours, but in severe cases even more may be taken. The excretion of alcohol by the breath is a good indication that too much is being given.

Conditions of the Nervous System. — Headache may be very troublesome and too often is little helped by treatment. The constant application of the ice-bag is often useful. Small doses of codeia (grain $\frac{1}{4}$, 0.016 gm.) may lessen it. If the coal-tar products are given small doses should be used. If these do not relieve the pain and the patient is unable to sleep on account of it, a small dose of morphine may be given

hypodermically. This is usually better than giving opium by the mouth.

Delirium is best treated by hydrotherapy, especially the baths, which improve the mental condition, quiet restlessness, and are usually effectual without drugs. An ice-bag should be kept constantly on the head of a delirious patient and cold affusions applied while in the tub or being sponged. Special efforts should be made to induce these patients to take large quantities of water and so favor elimination. Great care should be taken to watch a delirious patient constantly and he should never be left alone, for one cannot tell at what moment such a patient may get out of bed, perhaps only to wander aimlessly about the room but in other cases to try to escape. Even when apparently completely prostrated a patient may be capable of great exertion, and it is not safe to relax watchfulness because he seems too feeble to move. The draw-sheet is often enough to keep him quiet; it should come up to the chin with the arms underneath. If there be great difficulty in controlling the patient, it is well to use one of the forms of restraining sheets, which is better than struggling with him. A dose of morphine hypodermically (gr. $\frac{1}{4}$, 0.016 gm.) is usually advisable. When there is marked restlessness it may be difficult to keep the patient in bed, and for such it is well to have a board or canvas along the side of the bed to prevent his falling out. It may be difficult to give the tubs to such a patient and frequent wet packs may be substituted. In hospitals it is well to have small rooms with wire screens on the windows for delirious patients.

Drugs may be of help in such conditions. The bromides with small doses of chloral and codeia may be given but in serious cases it is better to use morphine hypodermically. It is well to remember the importance of sleep for these patients. The patient may thrash around in delirium or lie quietly in coma vigil and for days not be asleep. Probably the best thing we can do for such patients is to give enough morphine hypodermically to secure some hours of sleep. The rare attacks of maniacal delirium are best treated by morphine hypodermically and the gentlest restraint that is effectual.

Lumbar puncture is advisable for all patients with delirium or profound stupor. It is important for diagnosis but also for treatment. If fluid is obtained on puncture it may be allowed to run as long as it comes with any pressure, but it is probably well not to withdraw more than 20 cc. at one time. The puncture may be repeated daily if necessary, but the amount of fluid obtained and the relief given are the best guides for its repetition.

Alimentary Tract.—Reference has been made to the care of the mouth. If the lips are dry, glycerin may be frequently applied. Special care should be taken to keep the mouth clean and to encourage the patient to clear the throat. The complications which occur in the salivary glands are best treated at first by the application of an ice-bag. If there be signs of suppuration an incision should be made, but in parotitis it may be advisable to relieve tension before there are positive signs of pus formation. In the rare cases in which extensive cellulitis of the neck occurs, serious obstruction to the breathing may appear suddenly and

the instruments for tracheotomy should be at hand. If there be signs of laryngeal lesions, the mouth should be frequently cleaned, the patient's head kept low, the atmosphere of the room kept moist and preparations made for tracheotomy, which should be done before marked signs of obstruction appear.

Stomach.—Fortunately there are few gastric symptoms which need special treatment. Nausea and vomiting are rare and if due to disturbance of the stomach itself it is well to cut down the diet to albumin and water or water alone. Small doses of sodium bicarbonate and bismuth subnitrate (āā gr. 10, gm. 0.6) may be given; lavage is often helpful if the symptoms be severe. There are some patients who are never able to take more than a given amount of liquid at one time without nausea or regurgitation and this limit has to be carefully observed. Sometimes with meteorism the stomach is enormously distended. The stomach-tube gives immediate relief and may be passed every few hours as long as the condition lasts. This is especially advisable if the distension is interfering with respiration.

Intestinal Meteorism.—A simple diet with large amounts of water is an important preventive, but constant watch should be kept for meteorism, and treatment begun at once instead of waiting until distension is marked, for a slight amount will often diminish with care in the diet and the giving of a turpentine enema (30 cc. of turpentine to 500 cc. of warm water), and by these means any increase may be prevented. When distension is marked, the diet should be reduced to albumin or water only. A large flat ice-bag should be applied to the abdomen. Of drugs, turpentine is the most useful and may be applied locally by stupes or given by mouth or in an enema. The turpentine stupes are very useful; they may be applied frequently, but it is wise to alternate them with stupes wrung out of hot water as the constant application of turpentine may cause severe local irritation. By mouth the usual dose of turpentine is ♏15 to 20 (1 cc.) every four hours, but this should not be given continuously for more than forty-eight hours and the urine should be carefully watched, large amounts of water being given at the same time. In patients with nephritis it is wiser not to give turpentine by mouth. When turpentine is given by rectum 1 or 2 ounces (30 to 60 cc.) may be added to a simple enema and care should be taken to see that it is thoroughly mixed with the water. The oil of cinnamon in doses of ♏3 to 5 (0.3 cc.) may also be given by mouth and charcoal and β-naphthol are sometimes of help. Eserine may be given hypodermically in doses of grain $\frac{1}{50}$; in my expericence the results have been disappointing.

The rectal tube may also be used. This should be passed gently for a distance of twelve to fifteen inches, but great care must be taken to avoid any undue force and only a soft tube employed, as ulcers in the rectum or lower colon have been perforated by a tube. It is usually well to leave the tube in position for about half an hour, turning the patient several times. With some patients, especially if there is a tendency to distension, it is advisable to give a turpentine enema occasionally.

Constipation.—This is to be desired. If the bowels do not move, a simple or oil enema should be given every second day. The possibility of fecal impaction should be kept in mind and if it occurs the usual treatment should be employed.

Diarrhœa.—This is best avoided by not giving purgatives and by a simple diet. When present it is well to cut off everything except albumin water by mouth and in severe cases give water only. Large doses of bismuth (gr. 30, gm. 2) or acetate of lead (gr. 2, gm. 0.13) may be given by mouth every three hours. The aromatic chalk powder (gr. 30, gm. 2) is sometimes helpful but the astringents seem to be of little use. The question arises as to the advisability of giving opium. Distension is apt to occur with diarrhœa and this is favored by opium; perforation often occurs with diarrhœa and is rarely recognized if opium has been given. In some instances the giving of small doses of codeia by mouth has been useful, but in intractable cases the use of the starch and laudanum enema is most effectual. It will be found possible to deal with diarrhœa without giving opium in the majority of cases. With diarrhœa or incontinence of feces it is well to keep a large pad below the patient; by its use the soiling of the bedclothes can be lessened and the danger of bed-sores diminished.

Hemorrhage.—Small hemorrhages and those early in the disease rarely require any special treatment. In the more severe cases the first essential is absolute quiet,[1] generally best secured by a hypodermic dose of morphine, one-sixth of a grain usually being enough. The diet should be reduced to albumin water or all food may be discontinued, and it is better to stop stimulants if they are being given. A light ice-bag should be applied to the abdomen. The giving of drugs is of doubtful value. Ergot is probably more harmful than helpful. Adrenalin has been given by the mouth or rectum, while some advise giving small doses in a saline infusion (1 dram—4 cc.—of the 1 to 1000 solution being added to the salt solution). Styptics by mouth are of little value. Some writers advise the giving of turpentine in good doses (ℳ20, 1 cc. every three hours). The most difficult question is as to the advisability of giving opium. Its use is sanctioned by long custom but to what extent bleeding is lessened by its administration is a question not easy to answer. By giving opium we favor distension which in itself is a serious condition. Perforation frequently occurs with hemorrhage, and if opium has been given there is practically no chance of recognizing it before the onset of general peritonitis. As a rule the patients with hemorrhage seem to do better without opium.

The calcium salts may be given as a prophylactic measure, the coagulation time of the blood being taken in every patient, and if it be prolonged, calcium lactate in doses of 10 grains (0.6 gm.) is given three times a day for three days at a time. If hemorrhage has occurred it is always well to give it, for it can certainly do no harm and should be

[1] It is a question whether the rule in some clinics not to move the patient for some hours after a hemorrhage, even to change the sheets, is a wise one. There may be danger in severe cases from even turning the patient, but by leaving him on his back for any time bed-sores are almost sure to appear and it is usually possible to turn him gently without risk.

helpful when there is general oozing and perhaps also when the bleeding is from a large vessel. Injections of blood serum have been of value in some cases.

Should one use saline infusions after a hemorrhage? In case of very profuse bleeding with the patient exsanguine and in collapse, an infusion should be given, but as a rule the advisability of giving them is doubtful, because in some instances the infusion seems to bring on further bleeding. There need be no alarm about low blood pressure following hemorrhage; this is to be desired as it favors clotting. The use of saline injections as a routine after hemorrhage is not advised. In cases of very severe hemorrhage with the patient exsanguine there is no question of the value of *transfusion* and it is to be recommended in such cases.

It is advantageous to have constipation after hemorrhage and there is no need of moving the bowels for three days at least. For this an oil enema followed by a simple one is usually best.

Perforation.—The treatment of this condition requires no discussion —immediate operation is necessary. But diagnosis must go before treatment, and we should consider it as much a part of our therapeutics to be prepared to make the diagnosis promptly as to deal with it. There are some points which may be emphasized.

1. It is the duty of every man who is treating patients with typhoid fever to be as familiar as possible with the symptoms and signs of perforation. There are few men who have the opportunity of studying many cases of it, and if they are seen only at long intervals the impression of the essential features is forgotten. For this reason it is all the more important to study the abdominal conditions in typhoid fever.

2. The nursing staff should receive special instructions to report suspicious symptoms at once. These orders are best written out so that there can be no possible doubt. Special stress should be laid on any sudden abdominal pain or increase in pain previously present. Nausea or vomiting, a sudden increase in pulse or respiration rate, and any sudden change in temperature, either a rise or fall, are important. When suspicious symptoms appear, the patient should be seen at once. The symptoms immediately after perforation are often so characteristic that the diagnosis can be made more easily then than later on. This is one of the advantages of having the patients in a hospital, especially if there is a senior resident who has had more experience than the junior interne can have.

3. Careful records should be kept in every case. A patient with suspicious symptoms should be watched, the physician staying at the bedside, for the short recurring attacks of pain, so important in the diagnosis, may not last long enough for the physician to be called.

4. Friendly coöperation between the physician and surgeon is important. The surgeon should be given the chance of seeing all patients with suspicious abdominal symptoms, for it is only by such experience that he has a proper chance to judge intelligently of the condition. In a hospital there should not be any delay from red tape; to wait some hours for the visiting physician or surgeon to see the patient may throw away all chance of recovery.

Exploration should be advised in a doubtful condition and can be done under cocaine.[1] No exact rules can be given as to what symptoms and signs justify exploration, but knowledge of the abdominal conditions, constant observation and careful records all help to prevent needless operation. It may be impossible to put into words the reasons which govern one in advising delay or operation. Our endeavor is to recognize the perforation and not the resulting general peritonitis.

If a perforation is found, the condition present must determine the procedure. A clean-cut opening can be closed by a purse-string suture of fine silk, reinforced by "mattress" satures. Suspicious ulcers may be turned in by the same method. When the opening is closed, the omentum should be brought down over the point of suture. Drainage, for which gauze is best, should always be used if a perforation has been found and is advisable after exploration when no perforation is found, if there be deep ulcers which may perforate later. If there be much distension and general peritonitis, it may be best to bring the piece of bowel with the perforation into the wound and fix it there without any attempt at closure. If the bowel be friable and sutures do not hold, as happens rarely, excision of a part of the bowel and bringing the ends into the wound may be tried, but such cases are almost hopeless. It is wiser not to irrigate but to wipe away the exudate with gauze pads moistened with salt solution.

In all cases the element of haste in operation is important. Close the source of infection, wipe away as much exudate as possible, put in drains and get the patient off the table as quickly as can be done. The possibility of a second perforation or of intestinal obstruction afterward has to be remembered, and if the necessity arises even a desperate condition should not prevent interference, for recovery after three operations is an encouraging fact to remember. Even if the patient be admitted with general peritonitis due to perforation there may still be a chance of recovery, as two of the successful results in this series belonged to this class. In some patients there is no sign of healing in the incision. There is usually severe toxemia and the outlook is almost hopeless.

There may be peritonitis without perforation or a simple appendicitis may occur. The symptoms may not differ greatly from those of perforation, and exploration is indicated.

Cholecystitis.—In this "borderline" condition the question of treatment is a difficult one. Granted that cholecystitis is present, should the abdomen be opened and the gall-bladder drained? The majority of patients with this complication will recover without interference, others will as certainly die. The milder attacks tend to clear up spontaneously and if the patients are carefully watched, delay is usually safe, but there is always the risk of perforation. If the patient be conscious so that a correct idea may be obtained as to pain and tenderness, and if he is in

[1] When it has been decided to open the abdomen it is well to give morphine hypodermically (gr. $\frac{1}{4}$) at once. The abdomen can usually be opened under cocaine and if there be no perforation the incision can be closed with the patient little the worse. If a perforation is found, a general anesthetic can be given if necessary during the handling of the bowel.

a place where constant watching is possible and immediate operation may be done if perforation occurs, one can wait with some degree of safety. But there is always the risk of waiting too long and after one has lost a patient from so doing, there is more inclination to advise operation in severe cases. For the pain, an ice-bag or hot stupes may be applied but opium should not be given. Tapping the distended gall-bladder through the abdominal wall ought not to be done. If the symptoms be acute and the signs pronounced, especially if progressive, operation is the safer course. Opening and draining the gall-bladder can be done under cocaine. If there be doubt as to the condition, exploration is safer as it means little added risk, while delay may mean the same, or perforation may occur and the danger to the patient be greatly increased. The exact procedure after opening the abdomen must depend on the condition found but drainage is usually the safer course. It may be advisable to pack gauze about the gall-bladder and open it a few hours later.

Abdominal Pain. — This frequently demands treatment. Careful examination should always be made to determine its cause so that treatment may be as rational as possible. Thus if it be due to constipation or a distended bladder, it can easily be relieved or if from distension this can be diminished. The possibility of pain being due to some acute abdominal complication, such as perforation, cholecystitis, etc., must always be kept in mind. If no cause can be found we must use symptomatic measures; thus an ice-bag or turpentine stupes may be applied to the abdomen. If the pain is severe and persistent, small doses of bromide (gr. 15, gm. 1) and codeia (gr. $\frac{1}{4}$, gm. 0.016 may be given. If it is very severe and is not relieved by these measures a small dose of morphine (gr. $\frac{1}{6}$, gm. 0.01) may be given hypodermically, but the need for this is infrequent. It is better to give morphine than opium, for severe abdominal pain may be due to an acute abdominal complication and if opium is given the difficulty of recognizing this is greatly increased.

By giving opium for abdominal pain in typhoid fever many patients have gone to a comfortable death without a suspicion even being entertained that a complication, such as perforation, was present.

Respiratory Tract. — Severe epistaxis may be troublesome. The application of cold, the use of astringents, such as alum or adrenalin solution (1 to 1000) locally, is usually enough to control it, but occasionally it may be necessary to plug the posterior nares with gauze. The initial bronchitis rarely requires any treatment and with the bath treatment it usually clears up rapidly. If it be severe, small doses of a sedative expectorant may be given, but the majority do about as well without any drugs. Pleurisy should receive the usual treatment and an effusion should be tapped early and an empyema drained immediately. The prevention of the hypostatic type of pneumonia is most important. The bath treatment is a great help in this, but in addition the patient should be kept carefully turned from side to side. The importance of this should be frequently impressed on the nurse. When pneumonia is present the treatment does not differ from that usually given.

Circulatory System.—It is important to keep constant watch not only on the rate and character of the pulse but also on the sounds of the heart. The blood pressure record is also of value. When the pulse becomes rapid, 120 or over, and the first sound of the heart feeble, it is well to give strychnine, which may be begun by mouth in doses of grain $\frac{1}{50}$ to $\frac{1}{20}$ (gm. 0.001 to 0.003) every four hours. In serious cases it is better to give it hypodermically in the same or even larger doses. The patients stand the drug well and it can safely be given in full doses, even up to grain $\frac{1}{10}$ every four hours for a short time. If there be signs of an overdose, as shown by muscular twitching, etc., all that is necessary is to omit the drug for a few hours. With signs of a failing heart, alcohol is usually a help, and the patient may be given from 4 to 8 ounces in the twenty-four hours. In patients with a very rapid pulse and marked signs of cardiac failure the giving of digitaline hypodermically, in doses of grain $\frac{1}{30}$ (gm. 0.002) every four hours, is sometimes helpful. Tincture of strophanthus (♏xv, 1 cc.) or strophanthin (gr. $\frac{1}{100}$, gm. 0.00065) given intramuscularly is of value As a rule it is better not to give more than two doses in one series, but this may tide the patient over a critical period. Saline infusions are sometimes of use, an average amount of 500 to 700 cc. being given. In cases of sudden collapse, camphor (gr. 2, gm. 0.13, dissolved in olive oil) or ether (♏20 to 30, cc. 2) may be given hypodermically and repeated doses of the aromatic spirit of ammonia (dram $\frac{1}{2}$, cc. 2) by mouth.

Phlebitis.—The leg should be somewhat elevated and kept absolutely at rest on a pillow. The attendants should be instructed not to rub it and to exercise every care when movement is necessary. If may be wrapped in raw cotton and lightly bandaged. The lead and opium lotion may be applied locally. If there be severe pain, general sedatives and even morphine may be required. The patient should be kept quiet for some days after the acute symptoms have disappeared and the leg used very little for at least six weeks. It is well to have the patient wear a bandage for a time and later, if there be swelling, an elastic stocking.

Urinary Tract.—A common difficulty, especially early in the disease, is retention of urine. The necessity of frequent attention should be impressed on the attendants, for very often the patient feels no discomfort and does not ask for the urinal. Every effort should be made to avoid the need of catheterization, for it means added risk to the patient and additional work to the physician. If it has to be done great care should be taken to avoid infection. The catheterization should be done by the physician whenever possible, as too often in hospitals it is intrusted to the orderlies. If it has been necessary to pass the catheter, it is important to try to have the patient void within three or four hours after being catheterized. The attendants should wait on such a patient at least every three hours. It is well to give large amounts of water, for, as a rule, the more urine the less trouble with retention.

The occurrence of typhoid bacilli in the urine must be kept in mind. These have to be looked for, as they may be present without causing any symptoms. It is well to give hexamethylenamine (gr. 15, gm. 1) three times a day, to every patient with typhoid fever. The writer has

never seen any harm from its use, although some cases are reported. If bacilluria or cystitis be present, the drug should be given freely and with cystitis it is well to begin bladder irrigations of bichloride of mercury, at first of a strength of 1 to 100,000, gradually increasing to 1 to 50,000. The importance of not allowing these patients to go from under observation until the urine is completely clear of organisms may well be emphasized, and it should be part of our routine treatment to be certain that before discharging the patient, his urine is free from bacilli.

The Skin.—Constant care should be taken to keep this clean and special attention should be given to the dependent parts. After each movement of the bowels, the sacral, anal, and gluteal regions should be cleaned with a cloth wet with carbolic or bichloride solution. Dusting powder should be freely used. In patients who are very toxic and have incontinence of urine or feces the care of the skin is a most difficult matter. It is well to use a rubber urinal and keep large pads under the buttocks. When there are signs of redness in the sacral region, it is well to keep the patient on a ring or turn him frequently from side to side, and the rubbing with alcohol and the use of dusting powders should be kept up. One of the best local applications, at the first sign of redness, is a 1 per cent. solution of silver nitrate painted over the area. If any signs of breaking down appear, we should endeavor more than ever to keep the patient off his back, but it is well to remember that when a bed-sore has once begun it may be very difficult to check its course. There are many applications that may be used, perhaps the boric acid poultice, frequently changed, is as good as any. Dusting powders should be used and a constant effort made to keep the area as clean as possible. As a rule dry applications are preferable to ointments at an early stage, although the latter may be used with advantage when healing begins. If sloughs form they should be cut away at once, and it is well to remember that they may extend some distance under the healthy skin. The usual treatment of bed-sores is the same as that of such ulcers elsewhere.

Boils are troublesome complications, and as one patient may infect another, care should be taken that neither his sponge nor tub is used for other patients. As a rule early incision is best; this can be done under a local anesthetic and saves the patient a great deal of misery.

Ductless and Other Glands.—With the first sign of involvement it is well to put on an ice-bag or use hot applications. If there be signs of suppuration it is well to make a free and thorough incision early. Aspiration has been done in some localities, such as the breast, and has given relief, but if there is suppuration an incision is usually necessary.

Bone Lesions.—Occasionally these come on during the course of the fever. The application of an ice-bag often relieves the pain and periostitis may subside without any other treatment. The areas should be carefully watched and, if suppuration occurs, it is well to incise at the time and leave more thorough surgical treatment until after recovery from the attack. The occurrence of bone lesions in the spine (spondylitis) may give considerable trouble. Every effort should be made to avoid trauma; the patient should be moved very carefully and the back supported as well as possible. Strapping or bandaging may give some relief,

but if not a light jacket or some form of apparatus may have to be applied. The severity of the pain usually requires sedatives and it is necessary to give large doses to give any relief. If coxitis occur, the frequency of dislocation must be remembered and every care taken to prevent this by keeping the leg at rest, either by a long splint or sand-bags, and care should be taken with every movement of the patient.

Tender Toes. — The application of equal parts of alcohol and tincture of iodine has been found useful, while in some patients methyl salicylate applied locally has given relief. It is always well to put a cradle over the feet to remove the weight of the bedclothes.

Relapse.—The treatment of this differs in no way from that of the original attack. During a recrudescence it is safer to cut down the diet to liquids. The post-typhoid elevations as a rule require no special treatment.

Convalescence.—The return to solid food should be gradual and it is well to wait until the temperature is normal for some days before giving meat. Scraped beef and sweetbread may be given earlier. The smuggling of food by friends has to be guarded against. In all cases the condition of the patient and the character of the attack should be considered. With a coated tongue, a tendency to diarrhœa or after an attack with marked abdominal features, it is well to be especially cautious in returning to solid foods. After a protracted attack or if there be marked emaciation or a psychosis, it may be well to feed more liberally. There is no set rule; the dietary for each patient must be decided by the conditions present.

The patients may be propped up in bed usually from the seventh to the tenth day of normal temperature and allowed up in a chair three or four days later. It is well to have them out in the open air and sunshine as much as possible during convalescence. During this time they should be guarded against excitement and are better not to see many visitors. At first they should see only one a day and the number should be increased gradually. It is generally best not to allow the patients to read too early, certainly not before they are up in a chair. The patients with a persistent slight fever give considerable anxiety; this occurs most often in those who are very emaciated or neurotic. Discontinuing the taking of the temperature or doing so only once or twice a day is often all that is needed. In these patients, if there be no complication, one can increase the diet rapidly even if there be some slight fever. For constipation simple enemata or injections of olive or cotton-seed oil (300 cc.) may be given. If a purgative by mouth be needed it is well to give castor oil, half an ounce of which may be administered in the evening. The combination of the fluid extract of cascara and glycerin (of each a dram, 4 cc.) given two or three times a day is helpful. Subsequently cascara alone or compound licorice powder may be used. Diarrhœa during convalescence should always be regarded seriously, as it is often associated with ulceration in the colon and may prove very persistent. The diet should be carefully restricted, large doses of bismuth (gr. 30, gm. 2) or zinc oxide (gr. 5, gm. 0.3) given by the mouth and astringent injections used, such as alum, weak silver nitrate solution

(1 to 1000), etc. In very emaciated patients a daily oil rub is useful. Alcohol may be helpful in patients who are exhausted and recover slowly. Iron should be given, if there be anemia, as Blaud's pills.

There may be marked disturbance of the heart rate, either increase or decrease, especially after any exertion or excitement. These patients should be kept at rest, in bed or in a chair, until the pulse rate returns to normal or near it, and strychnine in good doses should be given. They should increase the amount of exertion very gradually and be cautioned against sudden effort.

An important matter to decide is the length of time that should elapse before patients return to work. With a laborer there is not much difficulty, as he is not likely to return to work until he is physically able. In the case of a professional man the matter is more difficult and the physician should be firm in insisting on a prolonged vacation. The length of this must depend on the character of the attack, but a minimum of at least three months should be given from the time the patient is convalescent, and in some cases six months will be required. If the patient is very nervous and easily upset by any mental exertion it may be a year before he is able to take up work again. Patients are frequently very much worried by incapacity for mental exertion, and loss of memory, both of which are common after an attack. The physician can give a good prognosis; time is the best treatment.

Another troublesome occurrence is the falling out of the hair, the likelihood of which is lessened by cutting it short at the beginning of the attack. Should it occur little can be done to check it, except the use of a stimulating hair lotion.

After a severe attack there may be swelling of the legs when the patient goes about, especially in the latter part of the day. It is well to keep these patients quiet until there is no return of the œdema when they go about on their feet. A bandage or elastic stocking may be used.

Sequelæ.—The bone lesions may appear at a long interval after the attack. Their treatment is strictly surgical and thorough excision of the diseased areas is necessary. Œsophageal stricture may be treated by dilatation or, if this prove ineffectual, by operation. The typhoid insanity is best handled by an alienist. If there be a definite psychosis after recovery from the attack of fever it is usually advisable to place them in an institution for the treatment of mental diseases. The post-typhoid neuritis offers no special peculiarities; massage, electricity, and strychnine internally are useful. Cholecystitis should be treated by the same methods as during the attack.

Carriers.—The treatment of these offers much difficulty. It is possible that the persistent free use of hexamethylenamine, especially toward the end of the attack, acts as a preventive. It is also of use in cases detected during convalescence, but is less likely to be of value in chronic carriers. Antiseptics diminish the number of bacilli when combined with low diet and purgatives in bowel cases and diuretics in urinary cases. In rare cases the administration of lactic acid bacilli has proved effectual and is worthy of trial. When the condition is chronic, drainage of the gall-bladder and *x*-ray treatment have been successful, but by

no means always so. The use of an autogenous vaccine offers the best chance of success. Various doses have been given, usually beginning with 25,000,000 to 50,000,000 and increasing to 100,000,000 to 500,000,000 bacilli, at intervals of about ten days. Vaccines would probably have a better effect if combined with diuretics in urinary carriers and *x*-ray treatment in gall-bladder cases. Care should be taken to prevent carriers from handling food supplies and they should be instructed in the care they should take. Carriers in whom treatment is unsuccessful should be under the supervision of the health authorities.

There are certain things which should be done as a routine in the daily examination of the patient with typhoid fever. The general condition, the temperature, pulse and respiration records, the mental state, the condition of the mouth and tongue, the character of the heart sounds and pulse, the state of the lungs, especially at the bases, and above all the condition of the abdomen as regards distension, tenderness, pain, extent of the respiratory movements and resistance or rigidity, should all be noted. With this the amount of urine and the number and character of the stools should be observed. It is an advantage if there be a record of the blood pressure and a count of the leukocytes every two or three days. The urine should be examined frequently and typhoid bacilli looked for. Should symptoms suggestive of a complication appear the records ought to be taken more frequently. The important points are simplicity in the method, care in the nursing and common sense throughout. We cannot abort the disease and we have no specific treatment as yet. Careful nursing, constant care, and an intelligent knowledge of our limitations and the evils of misdirected zeal, are all essential. The comfort of the patient and the necessity of being sure that he obtains sufficient sleep are important.

PARATYPHOID FEVER

In addition to the disease produced by infection with the typhoid bacillus we have somewhat different forms caused by allied organisms to which the designation paratyphoid fever is applied. These may be regarded as varieties of typhoid fever and included under that term as a general designation rather than considered as distinct diseases. The former seems advisable to the writer as their general characters are much the same.

Two varieties of paratyphoid fever are described: Paratyphoid A, due to *B. paratyphoid A* or *acidumfaciens*, and paratyphoid B, due to *B. paratyphoid B* or *alkalifaciens*. In Europe the latter is regarded as the more common, but in this country the former appears to be the more important. Thus in one European series of 800 cases of typhoid-like infection, 75 were instances of paratyphoid B, 11 of paratyphoid A, 6 of infection with colon bacillus, and in 30 there was a mixed infection with the typhoid bacillus and paratyphoid B, and in 2 with the typhoid bacillus and paratyphoid A. Paratyphoid fever B has a close association with meat poisoning, and the causal organism is by some regarded as

identical with *B. enteritidis* Gärtner; at any rate it is closely related. Certain German writers have gone to extreme lengths in making classifications of various forms of infection with these organisms.

Etiology.—There is no special difference from typhoid fever except in regard to the probability of infection from eating infected meat (paratyphoid B).

Pathology.—This is much the same as in typhoid fever, except that there is more tendency for superficial necrosis, as in dysentery, than deep ulceration to occur. The findings are much the same, except that perforation is extremely rare in these forms.

Symptoms.—These in general are much the same as in typhoid fever but usually with a milder course. Some of the cases which are of the "meat-poisoning" type (paratyphoid B) may begin very suddenly with marked gastro-intestinal disturbance which sometimes suggests cholera. The symptoms are usually most marked in the intestinal tract. The fever as a rule is not high. Practically every complication may occur as in typhoid fever, but perforation is rare. Hemorrhage is usually not profuse, if it occurs, and relapses are rare. The course is often shorter than in typhoid fever and the mortality is low, probably not more than 1 per cent.

Diagnosis.—This cannot be made from the clinical picture. It is absurd to lay stress, as some writers do, on special features—as the occurrence of herpes or a chill at onset—as diagnostic of paratyphoid fever. Nor can any mode of onset be regarded as characteristic. Typhoid fever has so many different modes of onset that it is not safe to draw any conclusions from variations in it. Specific agglutination reactions are of some value, but a positive diagnosis can only be made by finding the organisms in blood cultures or in those from the urine or stools.

Treatment.—This is essentially that of typhoid fever.

Manchurian "Typhus."—This is apparently a variety of paratyphoid fever which occurs in parts of Russia and Japan. The causal organism is agglutinated by the patient's serum in high dilutions. It is usually found in blood cultures during the fever. The eruption (roseola) is usually profuse. The death rate is low.

COLON BACILLUS INFECTIONS

Normal dwellers in the intestine, colon bacilli may, under certain circumstances, perhaps increased virulence or decreased resistance of the host, become pathogenic. It is probable that such infections are acute and chronic, the former often possible of proof, the latter sometimes a matter of surmise. The colon bacillus may cause a general infection in the form of a more or less distinct disease or as a terminal infection, or secondary infection as, for example, in the course of typhoid fever. It is possible that these general infections are more common than has been supposed. In other cases it may cause a local infection of one organ, which is especially common in the kidney. There is still a third group which may be termed a chronic infection. In these cases it may be responsible for widely different conditions. Thus some cases

of chronic nephritis may be due to such an infection. Some forms of anemia and cirrhosis of the liver may be caused by it and not improbably some of the cases of chronic arthritis. The colon bacillus may play a large part in the etiology of very different diseases.

It is convenient to consider the infections under several headings.

1. **General Infections.**—(*a*) An acute general infection occurs which may have features very much like typhoid fever and in some cases there have been epidemics of this form. The fever may be continuous for ten to fourteen days and recovery may be slow, as after typhoid fever. In these cases there is frequently a good deal of disturbance of the intestinal tract. It is possible that a certain number of cases of slight fever with gastro-intestinal disturbances are instances of this general infection. It is extremely difficult to form any idea as to how common such attacks are as without blood cultures the diagnosis is not made positively.

(*b*) In some cases there is a condition which is much like pyemia in that, following a general infection, there are local abscesses in different parts of the body. If these are confined to one organ or are only recognized in one organ, the general infection may be overlooked. It is quite possible that many cases of kidney infection really belong to this group and are not examples of infection of one organ.

(*c*) *Terminal Infections.*—It is not infrequent at the end of some chronic illness to have a general infection with the colon bacillus. The features of this are likely to be masked by the primary disease and, beyond some increase in fever, little may be noted. This is exactly analogous to the terminal infection caused by many different organisms.

2. **Subacute or Chronic Infections.**—It has been suggested that certain chronic diseases have their source in persistent colon bacillus infection lasting over a long period of time. Arteriosclerosis, cirrhosis of the liver, chronic nephritis, and chronic arthritis have all been suggested in this connection. It is evident that proof of the etiological relationship is difficult to give. There is not so much doubt regarding the influence of these infections in producing anemia. Following intravenous injections in animals, very marked anemia has been produced, and a picture much like that found in pernicious anemia. In these cases there was also marked change found in the cord rather analogous to that in pernicious anemia. It is possible that such an infection may be a factor in the causation of severe anemia in the human individual. It must be confessed, however, that the proof for these cases is not definite.

3. **Local Infections.**—(*a*) *Peritonitis.*—Either local or general peritonitis may be due to colon bacillus infection. This may follow perforation of the bowel, but also occurs in cases in which this has not happened.

(*b*) Infection of the *gall-bladder* and *gall-ducts* is probably not uncommon. The symptoms usually suggest some hepatic disorder. There may be leukocytosis and tenderness over the gall-bladder. In other cases the infection may be in the hepatic ducts, with more or less persistent fever, jaundice, local tenderness, and some leukocytosis.

(*c*) Infection of the *urinary* tract. This is the commonest site of local involvement. The infection may come by various routes; the

ureter, the blood, and the lymphatics. There is doubt as to the frequency of direct infection by the ureter, but it is more common in women than in men. Infection by the blood would seem to be a very likely method and in many cases in which the infection is regarded as local in the kidney it is probably secondary to general infection. There is much to support the view that the commonest method of infection is through the lymphatics, probably quite commonly from the bowels. A very slight abrasion of the mucosa of the colon allows the bacilli to enter the lymphatics. By this method infection of the right kidney occurs more frequently than the left, as there is a certain direct lymphatic connection between the cecum and ascending colon and the right kidney. It is important to realize that the infection of the kidney may occur alone or in another disease, as is seen especially with typhoid fever. In this disease we not infrequently have a pyelitis due to a colon infection.

There are several groups of cases which may be classified as follows:

1. Those in which pyelitis comes on in the course of or during the convalescence from another infection. In such cases after the temperature is normal, following a chill there may be an increase in fever. There is leukocytosis, frequently pain in the region of the kidney, and possibly enlargement of the organ. The urine shows pus, and colon bacilli may be obtained. These cases are comparatively common during convalescence from typhoid fever. If a blood culture is taken about the time of the chill, colon bacilli are often obtained.

2. An important group occurs in children and by far the largest number in females, as in 53 out of 60 in Jeffries' series. The infection at this age is often severe, as 9 out of 60 cases in this series were fatal.

3. With pregnancy or after delivery. This group is well recognized, and pyelitis, especially in the right kidney, is common.

4. In some cases an infection due to the colon bacillus occurs in newly married women, with urethritis, cystitis, and possibly a pyelitis. It is important to recognize this as unjustified suspicions of a gonococcus infection may be entertained.

5. There are cases in adults in whom a pyelitis and cystitis appear without any definite cause. A chronic pyelitis may result or secondary lesions such as arthritis.

(*d*) *Intestines.*—Probably many cases of diarrhœa are of this nature. The attacks of intestinal disturbance with malaise and fever, so common in those who enter an institution, are probably due to infection with a new strain of colon bacillus. The relationship to gastric ulcer and appendicitis is suggestive in some cases.

(*e*) Various organs may show inflammation due to infection with this organism. Meningitis, endocarditis, etc., are possible results.

Diagnosis.—This must depend on definite cultural findings from the blood in general infections and from the urine in the involvement of the urinary tract.

Treatment.—The usual measures for a general infection should be carried out. When in the urinary tract, large amounts of water, urinary antiseptics, local treatment, and the use of vaccines offer the best chance of aid. These should be begun as early as possible.

CHAPTER III

LOBAR PNEUMONIA[1]

By GEORGE WILLIAM NORRIS, M.D.

Synonyms.—Peripneumonia; peripneumonia vera—Sydenham (as opposed to peripneumonia notha—obstruction of the lungs by heavy, viscid, pituitous matter); pneumonic fever—Huxham; croupous pneumonia; lobar pneumonia; pneumonitis; sthenic pneumonia. German: Lungenentzündung; croupöse Pneumonie. French: pneumonie lobaire; fluxion de la poitrine.

Historical.—The relation between the clinical manifestations of pneumonia and consolidation of the lungs was pointed out by Morgagni, while Baillie described the morbid process as "hepatization." Further important studies were made by Laennec, Cruveilhier, and Rokitansky. The diagnosis of pneumonia, based upon the physical signs, is to be accredited to Auenbrugger and Laennec. Addison showed that the inflammatory exudate was intravesicular and not interstitial, while to Rokitansky belongs the credit of differentiating between lobar and lobular varieties. Joerg,[2] Bailly, Legendre and Bichat did much to distinguish the various forms of atelectasis or defective expansion from inflammatory processes.

Occurrence.—The actual frequency of pneumonia as compared with all internal diseases ranges between 1 and 6 per cent. In the United States during the census year of 1890, over 9 per cent. of all deaths were due to pneumonia, in 1900, over 10.5 per cent. Comparing the city with the country districts, the last-named census shows the proportion of the mortality per 100,000 of the population to be 233.1 and 135.9 respectively. In England and Wales in 1899 the death-rate from pneumonia was 125.5 per 100,000. Reports published in different parts

[1] Before writing the original article on croupous pneumonia the author endeavored to collect from the entire literature all the statistics which were available. The statements made are based upon the study of thousands of cases reported by observers in different parts of the world. The total number of cases available for the investigation of a given subject of course varied greatly, since the classification of different authors varied, as did also the individual subjects upon which data were furnished. The "collected cases" referred to in the text therefore represent the results of compilation from his own cases, as well as those of the literature in general. Owing to lack of space it has been impossible to reproduce the exhaustive tables giving an itemized account of the cases reported by different observers, or to include the references. The writer desires to acknowledge his indebtedness to Dr. Charles M. Montgomery and to Dr. Paul Lewis for assistance in the revision of these chapters.

[2] A more complete study of the historical aspect is to be found in Jürgensen's classical work in *Ziemssen's Encyclopedia;* also in Wells' article, *Journal of the American Medical Association,* February 9, 1889; and Neumann, *Krankheiten des Menschen,* 2d ed., i, 151.

of the world indicate that the frequency of pneumonia is steadily increasing. Among the possible reasons which may account for this are: increased use of alcohol, lessened amount of time spent out of doors, increased facilities for travel, and increased overcrowding in the home, the workshop, and places of amusement. On the other hand a number of papers have been written to show that these statistics are erroneous, and that the apparent increase has resulted from faulty returns of the cause of death, and the misinterpretation of figures. It may be conservatively stated, however, that the frequency of pneumonia is at least not diminishing.

Etiology.—1. **General Factors.**—(*a*) *Increased Virulence of the Microorganism.*—There can be no doubt that the virulence of given strains of the pneumococcus varies greatly from time to time. This fact no one who has seen many cases of pneumonia, or who is familiar with the literature can doubt. The organism apparently tends to increase in virulence with each passage through a human subject, just as it tends to decrease in virulence when cultivated artificially. These facts are particularly brought out when we investigate various epidemic outbreaks. At such times it has frequently been noted that in a given household the most robust member is the last to succumb, in other words he had sufficient immunity to withstand infection, until the virulence of the pneumococcus had been enhanced by the successive passage through the less resistant members of the family.

(*b*) *Annual, Seasonal, and Monthly Curves.*—The disease exhibits very marked exacerbations during certain years. The majority of cases occur between November and June, which is supported by the findings in 34,587 collected cases. A study of this subject has been made by Newsholme based on the statistics of different cities in various parts of the world, with practically the same conclusions. Hardie, who has investigated the problem in Australia, found that the greatest number of deaths from pneumonia occurred in August and September, which he attributes to the exhausting heat, and to the fact that when the air is dry it is a better carrier of microörganisms.

(*c*) *Geographical Distribution.*—Pneumonia is ubiquitous, but is less prevalent near the equator and near the poles than in the intervening zones. In hot climates it is most often encountered in elevated sections, in which sudden changes of temperature are frequent and marked, the broiling midday heat being rapidly replaced by cold nights.

(*d*) *Meteorological Influences.*—While there seems but little doubt that these have a distinct although indirect influence on the occurrence of pneumonia, and although a good deal of investigation has gone on in the endeavor to throw light on the subject, yet, owing to the complexity of the problem, an exact scientific solution of it is still unattained.

Most writers have attributed a predisposing potency to lowering of the temperature, but statistics can be adduced both to prove and disprove the etiological factor of cold. It must also be remembered that although cold and dampness may be predisposing factors, it is at the times when these conditions exist that people are most apt to live in crowded quarters, without sufficient ventilation, and that the chances

of direct infection are much increased, to say nothing of the fact that at such times the temptation to indulge in alcoholic stimulants is greater.

(*e*) *Epidemics.*—Accounts of supposed pneumonia epidemics go back nearly as far as written history itself. An exhaustive tabulation has been made by Wells,[1] who gives a list of epidemics extending back to 1440. It has been supposed by some that the plague of Athens, which destroyed one-fourth of the population, as well as the Black Death, which ravaged Europe during the middle of the fourteenth century, were forms of pneumonic infection. The most reasonable explanation of epidemics is an increased virulence on the part of the infective agent. Many of them are stamped with a distinct individuality of their own; for instance, in some diarrhœa may be a very prominent feature, or insomnia, intense prostration, jaundice, cerebral symptoms, dyspnœa, etc.

In the Alaska epidemic of 1881, with one exception, only natives were attacked. At Obersichte the disease was limited to children under five years of age; at Kimberly to the Kaffirs. In an epidemic in Boston in 1876 the onset was very insidious, the course prolonged, and hemorrhages common. In Ireland in 1854 and in Italy in 1898, the attacks were extremely mild in character. "In the epidemic of Deri Gazi Kahn, in which 40 out of 550 persons lost their lives in a few weeks, the local morbid process proceeded with the utmost rapidity through all the stages of inflammation to suppuration, abscess, and gangrene. Both lungs were usually affected, and after death were found to be, to a great extent, disorganized." (Wells.)

Epidemics have been observed in hospitals, in houses, in jails, in barracks, and on shipboard. Numerous cases are on record in which nurses and others in attendance upon those sick of pneumonia have contracted the disease. In some epidemics overcrowding and bad ventilation have been potent factors. Mendelssohn has reported instances in which patients were attacked by pneumonia soon after being placed in beds previously occupied by individuals ill with this disease. In one instance an entire family, five in number, died from pneumonia within two weeks.

Ballard has "reported 490 deaths due to pneumonia, caused in the most part by eating infected bacon. According to this observer, those who had the disease could transmit it to others who had not eaten of the meat, a fact which has been noticed in many other instances. After having been kept for several months the bacon lost its toxicity. This epidemic was known as the Middlesborough pneumonia epidemic."

The marked severity of some of the epidemics has been attributed to the association of the streptococcus with the pneumococcus (Rechi).

Infection from Animals.—Pleuropneumonia contagiosa is a disease well known to veterinarians. The disease occurs in barracks and livery stables, attacks chiefly the larger horses, and is transmissible from one to another either directly or by means of an intermediate host. Fraenkel relates an instance, in the spring of 1884, in which such an epidemic existed among the horses of the Westphalian Artillery at Minden. Soon

[1] *Journal of the American Medical Association*, February 23, 1889, and *Medical News*, May 20, 1905.

afterward an epidemic of pneumonia broke out among the soldiers which was limited almost exclusively to those individuals who came in intimate contact with the horses. Numerous similar epidemics occurring in the German army are on record. In one of them a microörganism was isolated from the bronchial secretions of the horse which was indistinguishable from the pneumococcus.

To sum up, we are forced to the conclusion that pneumonia is a transmissible disease, to be classified with the infectious fevers, and like them to be guarded against by the application of antiseptic principles; for although the virulence of its infectiousness is as a rule not very great, it is under certain circumstances undoubtedly capable of transmission from person to person.

2. **Individual Factors.**—(*a*) *Cold.*—It is generally believed that hunger, fatigue, and exposure to cold are predisposing factors; but that something over and above these is required is shown by the fact that very little pneumonia existed in Napoleon's army during the retreat from Moscow. Again pneumonia is very frequent in very early and in very advanced life, times at which the "cold" factor does not play an important role. The effect of cold upon the organism has been explained as causing a retention of waste products of metabolic activity, variation in blood pressure, slowing of the blood stream, impairment of cellular metabolism, and reflex action. Among 4244 cases collected by the writer, 755 (17.79 per cent.) gave a history of exposure and "catching cold."

(*b*) *Trauma.*—Although the existence of "konkussions-pneumonie," as described by Litten, has been questioned by a number of authorities, there seems little doubt that trauma may and does in a certain proportion of cases have a distinct etiological influence. Souques[1] has reported 49 cases of typical croupous pneumonia following contusions of the thorax without actual injury to the lung tissue. These cases usually occur after direct blows upon the chest, or injuries produced by falling weights, or crushing force. Pneumococci have been found in the lungs in a number of cases, although in the majority the burden of proof was placed upon the occurrence of these organisms in the expectoration. It has been stated that cases of traumatic pneumonia show an increased amount of blood in the sputum. A case of traumatic pneumonia due to contrecoup has been reported by Lesieur, Froment, and Garin.

Among 6790 cases collected by the writer, 58 (0.85 per cent.) gave a history of injury. Baeck, who found 5 such cases among 340, noted a very high leukocytosis, the percentage of fatalities being, however, much the same as in other cases.

(*c*) *Immersion in Water.*—Fraenkel has seen about one dozen cases apparently due to this cause. Many of these terminate favorably. Norris reported a case of a stoker who jumped overboard into the Delaware river in midwinter; he was brought into the Pennsylvania Hospital with a temperature of 94° F. and physical signs of pneumonia; recovery followed. Among 830 cases collected by the writer, 66 had received a wetting (7.9 per cent.).

[1] *Presse Médicale*, 1900, vii, 109.

(*d*) *Aspiration Pneumonia.*—Stubenrath,[1] from experiments with animals, concludes that this form of pneumonia is dependent upon mechanical influences of aspiration without regard to the fluid used.

(*e*) *Inhalation Pneumonia.*—Pneumonia has been reported as the result of inhaling irritating substances such as dust, ether, and nitric acid fumes. The latter produce a rapidly fatal œdema of the lungs. Most of these were of the lobular type.

(*f*) *Occupation.*—This plays an etiological role. Gründler states that the recruits of Magdeburg are very predisposed to pneumonia until they become accustomed to their work. Emigrants are more susceptible than natives who have become acclimated. The United States census report shows that whites of foreign birth are much more frequently attacked than the native born. Outdoor occupations show a higher morbidity from this disease than indoor vocations.

Different races of men have in the course of centuries developed well-marked and distinct characteristics, which have fitted them to live in given localities. When a man emigrates to other degrees of latitude than those for which his heredity fits him he falls an easier prey to disease than the native. This is well exemplified in the case of the Lapps, who whenever they move from the frozen north to a temperate zone almost invariably die of pneumonia within a short time.

Sanitation is also of importance and closely allied with the question of cleanliness is that of ventilation. Pneumonia is distinctly more prevalent in cities than in the country, despite the fact that outdoor work preponderates in the latter, indicating that poor hygiene and overcrowding, with the attendant danger of infection, are more important factors than climate and temperature. Anders found the highest mortality from pneumonia in Philadelphia in the most densely populated wards, and in those occupied by negroes and foreigners.

The death-rate is considerably higher in the negro than in the white man; and higher for indoor than for outdoor occupations.

(*g*) *Alcoholism.*—Alcoholic intoxication seems to be a predisposing cause. Of 2407 cases collected by the writer, 130 were intoxicated at the time the pneumonia appeared. Karlsson's statistics show 10 per cent. of pneumonia cases among 11,267 alcoholic male patients, and 4.9 per cent. among 10,840 females. Doubtless the exposure incurred at such times contributes to the development of the disease.

(*h*) *Previous Attacks.*—Among the writer's cases collected in reference to this subject, 1615 out of 11,811 had previous attacks (13.6 per cent.). The writer found 56 cases in 500 who had more than one attack. Instances of an individual being attacked by pneumonia four times have been recorded. Chomel saw pneumonia in the same individual ten times, Frank eleven times, and Rust recorded an instance of a person being attacked twenty-eight times. There seems to be no doubt that recovery from each attack of pneumonia makes a subsequent one still more likely. In a certain number of cases, however, successive attacks seem to be milder in character.

[1] *Ueber Aspirations Pneumonie*, etc., Würzburg, 1898.

(*i*) *Acute Illnesses: Influenza.*—Pneumonia is well known as one of the most fatal complications of influenza. Epidemics of these two diseases often occur together. In a certain number of cases when they occur coincidently, the pneumonia is of the lobar variety, and is in no way distinguishable, macroscopically or microscopically, from typical croupous pneumonia (Fraenkel). Apparent cases of influenza, however, may be due to the pneumococcus and not to the influenza bacillus. Thus Curschmann states that in 49 cases of apparently typical influenza, the pneumococcus was isolated in 46, and the influenza bacillus was never found.

Typhoid Fever.—There is much confusion in regard to the relationship between typhoid fever and pneumonia. Undoubtedly many cases clinically classed as "typhoid pneumonia" are really forms of tuberculous disease. Others again are due to the typhoid bacillus. Among 4459 cases of pneumonia collected by the writer, typhoid fever was coincidently present in 64 (1.4 per cent.). Typhoid fever may predispose to pneumonia by lowering the general bodily resistance.

Pulmonary Tuberculosis.—Does pneumonia favor the development of tuberculosis? Is tuberculosis greatly aggravated by pneumonia? Do the two conditions frequently coexist? There is probably frequent confusion between the two diseases. On the one hand, apical disease of pneumococcic origin, if there be delayed resolution, may closely simulate tuberculosis. On the other hand, tuberculous pneumonia, in which the pneumococcus plays no part, is of frequent occurrence and may, under certain conditions, resolve to a remarkable degree, for a time, at least, and, if "consumption" subsequently develops, gives rise to the belief that a pneumonia was the cause of a *locus minoris resistentiæ.* It is well, therefore, to "be suspicious of an atypical pneumonia."

Chatard has reported that out of 658 cases of pneumonia, 9 were associated with pulmonary tuberculosis. Among 4466 cases of tuberculosis treated at the Phipps Institute in Philadelphia, during the first five years, 794 gave a history of having had pneumonia (17.8 per cent.). How many of these attacks, however, were true pneumonias, and how many were tuberculous in origin, cannot be stated.

Louis stated that a pneumonia engrafted on a tuberculous lung may "terminate rapidly and favorably." Walshe says: "If the lungs already tuberculized become actually inflamed, convalescence from the pneumonia often takes place as rapidly as if the lungs had previously been sound. . . . Some of the most marked examples of rapid resolution I have met with were in phthisical persons." In some cases the pneumonia does not seem to have much effect on the tuberculous process, but it frequently happens that a rapid disintegration of pulmonary tissue, or a generalized miliary tuberculosis promptly follows.

Regarding the increased activity of a tuberculous process which occurs at times after an attack of pneumonia, Cornet suggests that "the exudation of the latter disease may, as it were, wash out and destroy the areas of peripheral resistance of those tubercles which lie within its focus."

(*j*) *Chronic Diseases.*—*Diabetes.*—There is a marked discrepancy among the figures of different observers as to the frequency with which

pneumonia occurs in patients with diabetes mellitus. There seems to be no doubt, however, as to the higher mortality of pneumonia when complicated by diabetes. Diabetes mellitus occurred in 2 of my 2949 collected cases. Severe complications such as pulmonary gangrene not infrequently occur when pneumonia attacks diabetic subjects.

In other chronic diseases, such as *nephritis, arteriosclerosis, hepatic cirrhosis,* and the like, pneumonia often supervenes as a terminal infection, and the same may be said of diabetes mellitus. Anders, who has investigated the frequency of *cardiovascular lesions* in pneumonia at the Philadelphia General Hospital, found that in 275 autopsies on individuals dead of this disease, such lesions existed in 250, or 90.9 per cent., most of which were chronic endocarditis and endarteritis; whereas these lesions were found at autopsy, death being due to different causes, 380 times in 1600 cases (25 per cent.). It is very common for hemiplegic patients to die of pneumonia, and not infrequently the lung on the paralyzed side is attacked.

(*k*) *Age.*—This plays a well-defined role both in the frequency and mortality; 40.2 per cent. of 32,681 cases collected by the writer occurred between ten and thirty years of age.

(*l*) *Sex.*—Of 12,098 cases collected by the writer, 8881, or 73.41 per cent., occurred in males and 3217, or 26.59 per cent., in females. In adult life the incidence is usually estimated as 6 to 4, for male and female respectively. In early life this difference does not seem to exist, which would indicate that the greater exposure entailed by male occupations is the main factor in the difference.

(*m*) *Race.*—The negro race appears to be more susceptible to pneumonia than the white. The American Indian and the Esquimaux also seem to be very susceptible, whereas the Malays, and the natives of Hindoostan and Burmah, as well as the Chinese, have much more resistance. Again, there is considerable difference in different branches of the same race, thus the Celt is more susceptible than the Teuton.

(*n*) *Insanity.*—Pneumonia, according to Krafft-Ebing, is the cause of death in one-sixth of all cases of insanity. This includes the hypostatic types so often seen in marantic dements and in the pneumonia of vasoparesis met with in paralytics (Gaye). In the insane, pneumonia is very apt to have an insidious onset, and to run a symptomless course, save for such manifestations as anorexia and weakness.

Bacteriology of Pneumonia and the Pneumococcus Infections.—The study of the infectious nature of pneumonia dates from the observations of v. Jürgensen in 1874. Long before routine bacteriological investigations were begun, he placed pneumonia among the infectious diseases and assumed it to be due to a specific cause. He also regarded it as a general disease with local manifestations in the lung. In 1883, Friedländer announced the discovery, in pneumococcic exudates, of an organism termed by him the pneumococcus, which was capable of causing pleuropneumonia in mice and occasionally in guinea-pigs. Later investigations, however, demonstrated this organism to be an encapsulated bacillus, now generally known as Friedländer's pneumobacillus, but infrequently associated with lobar pneumonia.

The microörganism which has been shown to be constantly associated with acute fibrinous pneumonia was first thoroughly studied by Sternberg, in 1880, though its relation to pneumonia was not appreciated by him at that time. To this organism he gave the name of *Micrococcus pasteuri*. At about the same time Pasteur found an identical diplococcus in the saliva of a child suffering from hydrophobia. Although Sternberg's observation antedated that of Pasteur the discovery is credited to the latter by priority of publication. A little later, interesting observations were made by Talamon but it was not, however, until 1884, as the result of the labors of A. Fraenkel, that this organism was shown to have a definite and constant relation to pneumonia. Fraenkel isolated it from the sputum of individuals suffering from pneumonia, demonstrated its constant presence in the solidified lung, and, with pure cultures, produced exudative lesions of the lungs in mice and guinea-pigs and general septicemia in rabbits. He stated definitely that it was in all probability the causal agent of pneumonia.

The routine examinations of Weichselbaum (1886), Netter (1890), and others have demonstrated this organism to be so constantly present in the exudate of genuine acute lobar pneumonia that it may be considered as the chief etiological agent. Other organisms are occasionally associated with the pneumococcus, such as the *Streptococcus pyogenes*, the *Staphylococcus pyogenes aureus*, the *Bacillus diphtheriæ*, the *Bacillus influenzæ*, the *Bacillus typhosus*, and bacilli of the group of *Bacillus capsulatus mucosus*. Atypical courses, complications, and untoward results are the rule in these cases. Lobar pneumonia, moreover, may rarely occur in the absence of the pneumococcus, it being produced by the pneumobacillus of Freidländer, streptococci, and in one reported case by the colon bacillus. Lobar pneumonia caused by other bacteria than the pneumococcus is apt to follow an atypical course, with unfavorable features and complications, and shows a tendency to appear in epidemic form. Pneumococci may also be the only cause of pneumonia in certain infections, for example, erysipelas, diphtheria, typhoid fever, and influenza.

Morphology and Cultural Characteristics of the Pneumococcus.—The organism usually appears in the form of small cocci, arranged in pairs; generally lancet-shaped, with the blunt ends in apposition, at times oval or round, each pair or diplococcus being surrounded by a capsule. The diplococci frequently appear in chains, which are characteristically short, containing only four to six elements. The effect of certain culture media and other influences may so modify its shape and size as to render the bacterium almost unrecognizable. The pneumococcus stains readily with aniline dyes. Gram's method stains all but the capsule. Depending on the method used the capsule appears either faintly stained or simply as an oval halo around the two cocci. In sputum or fresh exudates the capsule is much more frequently present than in cultures on ordinary media. The organism can be cultivated readily on all culture media except potato and gelatin at a temperature of 18° to 25° C., and grows more luxuriantly on slightly alkaline media. On the surface of gelatin at a temperature of 24° C. the colonies appear as small round circumscribed

finely granular white or grayish points, which never liquefy the gelatin. On agar slants, at the temperature of the body, the colonies are transparent and delicate and scarcely visible to the naked eye. Growth in milk is characterized by acid production and coagulation of casein. In Hiss' inulin-serum-water medium the pneumococcus causes coagulation, and this medium is therefore of importance in differentiating the pneumococcus from the *Streptococcus pyogenes*, which under some circumstances may closely resemble it morphologically. For growing virulent organisms the proper temperature varies between 25° and 42° C., the optimum temperature being 37° C. (Neufeld and Händel).

The pneumococcus though remaining alive for months in dried sputum is readily killed by ordinary methods of disinfection. A temperature of 52° C. maintained for ten minutes is sufficient to destroy it (Sternberg).

The special points given by Neufeld and Händel in the differential diagnosis of freshly isolated and virulent pneumococci are the characteristic form and arrangement of the cocci, the capsule, the appearance in short chains, the defective or negative growth on gelatin at a temperature of 18° C., the poor hemolyzing capacity, the œdematous swellings produced by inoculation into the ears of dogs, the rapid destruction by bile and its salts, and the marked pathogenicity for dogs and mice.

The Pneumococcus in Apparently Healthy Individuals.—Since Sternberg demonstrated the presence of the pneumococcus in his own saliva many observations have been made concerning its frequency in the buccal secretions from normal individuals. Netter found it in 20 per cent. of the persons whom he examined, and investigators of the New York Commission report its presence in from 46 to 85 per cent. Pneumococci virulent for dogs have been reported to be found in 15 to 20 per cent. of cases in the saliva, and Gamaleia claims to have been successful in over 50 per cent. of cases. Pneumococci have also been recovered in healthy persons from the nose, pharynx, deeper air passages, and also from the bronchial secretion and from the conjunctiva. They have been reported to occur in the lungs of healthy children and even in urine. The question of town or country habitation or of indoor or outdoor occupation appears to make little difference in the frequency. A higher percentage of atypical strains was obtained from healthy persons than in those suffering from pneumonia.

Buerger's studies show that the organism is slightly more frequent in males than females and is most frequent in children. It may persist for considerable periods of time. Longcope and Fox found the percentage of the typical forms to increase rapidly in December and January and to fall off gradually in March and April. Virulent forms are naturally not so common in normal individuals, as in pneumonia or in convalescence from pneumonia. It is generally conceded that pneumonia does not usually arise from infection from without, but that these organisms dwelling harmlessly on the mucous membranes of healthy people, a normal habitat, reach the lungs, and there in coöperation with other factors summed up in the general term "predisposition," acquire the capacity to penetrate the tissues and give rise to the disease, pneumonia.

The interesting and practical question as to how long the pneumococcus may remain in the blood after an infection has been investigated by Tizzoni and Panichi.[1] It was found that the organism could be recovered from the blood as late as two hundred and nine days after inoculation. It seemed to make no difference whether an active or passive, a complete or partial immunity had been developed previous to the inoculation or not, although the amount of the virus used did seem to exert a direct influence—the larger the dose, the longer did the organisms remain in the blood. The pneumococcus appeared to require a longer time for its destruction in animals naturally susceptible to it (rabbits) than in those which possess a certain amount of natural immunity (asses and sheep). It was also found that in some animals infection was unattended by symptoms of illness, but that if a trauma was inflicted localized infection occurred at the point of injury and sometimes ended fatally. These observations throw an interesting light on traumatic pneumonia, especially in relation to Edsall and Ghriskey's case, in which pneumococci were recovered by culture from the blood of a man who had no pulmonary symptoms and in whom no history of an antecedent pneumonia could be obtained. Pneumococcemia or the presence of the organism in the oral and respiratory passages of many apparently healthy people, therefore, explains how temporary reduction of individual resistance brings about pneumonia. It is also possible that recurrent attacks of pneumonia may arise from the fact that after the first attack the pneumococci were never entirely eliminated from the blood. S. M. White[2] has reported a case of fatal meningitis due to the pneumococcus in a patient who had had pneumonia two years before, in whom no other portal of infection could be discovered.

The Pneumococcus Outside the Body.—The pneumococcus is a distinctly parasitic organism and outside the body has only been found in the dust and sweepings of rooms and other places where dried sputum may collect. Wood has made a very extensive series of experiments to determine its viability. He found that in sputum preserved in a moist state, if not exposed to direct sunlight, it may survive a considerable time, the average duration being less than two weeks. In the dried powdered sputum the organism if exposed to sunlight or diffuse daylight dies in an hour; if kept in the dark, in about four hours. Under the ordinary conditions of the sick-room the pneumococcus becomes harmless in about an hour and a half. The danger of infection except for those in direct contact with the patient may be entirely avoided, it would appear, by ample illumination and ventilation of the sick-room.

Toxic Products.—Little is known of the metabolic productions of the pneumococcus. The toxic substance is probably an endotoxin; that is, it does not appear in soluble form in fluid media in which the organism is grown, but is intimately bound to the cell body. It can be extracted in various ways from large masses of microörganisms. The freeing of the toxin in the living body is supposed to be due to the disintegration

[1] *Centralbl. f. Bakt. Parisit. u. Infekt.*, 1905, xxxvi, 25.
[2] *Journal of the Minnesota State Medical Association*, 1907, xxvii, 91.

of the bacterial cells. On the other hand, the possibility of the production of a soluble toxin in the living body cannot be denied. The difficulty of readily procuring a toxin of the pneumococcus hinders the successful production of antisera for this organism. By vaccinating animals with attenuated pneumococci or injecting extracts of the organism it is possible to produce a serum which in laboratory experiments will protect susceptible animals against many times the minimum fatal dose of virulent pneumococci. This serum is neither bactericidal nor antitoxic but belongs to a third group of antisera which appear to act through the agency of phagocytic cells. Such sera have the power to produce some change in the cocci which causes them to be more readily engulfed by the phagocytes. The element which causes this is termed an opsonin (Wright and Douglas).

The Nature of the Intoxication.—"It is possible (1) that the intoxication in pneumonia may be due entirely to disturbances in the metabolism of the body, and the growth of the bacteria may be only an inciting factor in these disturbances; (2) that the intoxication arises from the breaking down of the exudate at the site of the local lesion." In so far as the true pneumococcus toxin is concerned, sufficient experiments have already been made to show that there is no active soluble toxin formed in the cultures of pneumococcus. Experiments to detect free poisons in the filtered blood of infected rabbits were negative. The experiments of Friedberger in relation to the production of the so-called anaphylatoxin with pneumococcus were confirmed by Cole. Later Rosenow showed that acute intoxication could be produced in guinea-pigs by the injection of bacteria which had been allowed to undergo autolysis in salt solution. Similar observations were made by Neufeld and Dold. Cole's results with this method of producing a poisonous substance from the pneumococcus were somewhat inconstant. In certain cases the autolyzed extract produced symptoms and death like that seen in anaphylactic shock, but in other cases the effect was slight.

"In order to learn more in regard to the nature of the changes which the bacteria undergo and also to discover a method by which such poisonous extracts can be prepared more quickly and with great constancy, treatment of the bacteria with various chemicals was undertaken, but the results were not promising until we tried dissolving the bacterial bodies in dilute sodium cholate solution. It was found that such an extract of the bodies of the pneumococcus is extremely toxic when injected into rabbits and into guinea-pigs, and, furthermore, that the symptoms produced both in rabbits and guinea-pigs are exactly like those seen in acute anaphylactic shock in these animals after a second injection of horse-serum. In certain cases these symptoms have been produced by extracts which have been obtained by treating the pneumococci with a dilute sodium cholate solution for only ten minutes at 37° C., or half an hour at 4° C. Lately the view has been most generally held that the intoxicating substances obtained from the bacterial bodies arise by partial digestion of the protein substances of the bacterial bodies. While our experiments do not disprove this view, the short time and low temperature necessary for the setting free of the poison

would rather suggest that the intoxicating substances are preformed in the bacterial cells and are set free on their dissolution. These experiments would therefore rather tend to support the older endotoxin theory of Pfeiffer. The toxic substance so obtained is labile, being destroyed at 60° C. for one hour" (Cole[1]).

The Opsonic Index.—Rosenow, who has studied the phagocytosis of pneumococci *in vitro*, found that non-virulent strains are readily taken up by human leukocytes in the presence of normal serum, the phagocytes being roughly proportionate to the amount of serum present. Washed leukocytes do not take up the pneumococci. Virulent strains are not taken up under any conditions until attenuated by cultivation. Pneumococci isolated from the patient's blood before, during, or after crisis are not taken up by the patient's serum *in vitro*, nor by normal serum. His investigations point to the fact that during and shortly after the crisis there is a slight increase in opsonic power; and that in fatal cases this may fall below normal. Pneumonic leukocytes are more phagocytic than normal ones, as well as more resistant to heat. The pneumococcidal action of pneumonic or other blood is due to the combined action of the serum and the living white corpuscles. The serum alone has no bactericidal action on pneumococci.

Wolf, who also studied the opsonic index, found this feature decreased in the early stages of pneumonia. In favorable cases the index rose as the crisis was approached, while it remained persistently low in fatal cases. The total antipneumococcic index—as estimated from the leukocytic and the opsonic indices—was increased early in favorable cases, and remained high until the crisis had occurred. The experimental injection of dead virulent pneumococci brought about a similar evolution in the antipneumococcic index in normal individuals; but dead avirulent pneumococci were apparently without effect upon the opsonins.

One attack of lobar pneumonia is commonly stated to afford very little if any protection from subsequent attacks. None the less, most of the immunity phenomena, as represented by the reaction of the elements of the blood, can be demonstrated in greater or less degree as concerns the pneumococcus.

The human being possesses a considerable degree of natural immunity against pneumococcus infection. The mechanism of this natural defensive mechanism is imperfectly known. Opsonins undoubtedly play some part, and thermostabile bactericidal substances are also to be demonstrated in the blood plasma.

A marked degree of active immunity can be developed by repeated treatment of animals with cultures of the pneumococcus. The serum of the actively immunized animals when transferred to normal animals confers a fair degree of passive immunity, and may, under carefully chosen experimental conditions, be made to operate as an efficient therapeutic agent.

The serum of pneumonia patients after the crisis can also be shown to have protective properties against experimental pneumococcus in-

[1] *Journal of the American Medical Association*, 1912, lix, 138.

fection. The presumption is that serum, in combating experimental infections, acts in some way to strengthen the bodily resistance of the animal. It has been shown by Neufeld that the relation of amount of serum to body weight is more important than that of amount of serum to amount of bacteria injected. While toxic substances can be extracted from the pneumococcus, the sera are probably not antitoxic. Even the question as to the place of the toxins so extracted in the production of the natural disease is unanswered.

The attempts to establish an efficient serum therapy for lobar pneumonia have so far failed of satisfactory result. The most recent experimental work, especially that of Neufeld and his co-workers, indicates that the doses so far used have been much too small. It is also likely that methods for producing a sufficiently potent serum on a large scale have yet to be perfected. Hope for a future treatment along these lines may well be maintained.

The recent results of Morgenroth with ethylhydrocuprein, indicate that there may be some prospect of a specific chemo-therapy for pneumococcus infections.

The Pneumococcus in Non-pulmonary Lesions.—In the complications of pneumonia such as pleuritis, pericarditis, endocarditis, and meningitis, the pneumococcus is practically always present. These secondary lesions are to be explained by direct extension, passage along lymphatics, or by a general invasion of the blood stream. Other organisms than the pneumococcus may be present and, in some instances, the complications may be due to an independent secondary infection. The pneumococcus, however, is responsible for most of the complications. It is capable also of producing lesions of various organs in the absence of a primary lesion in the lung. Thus, it has been found in peritonitis, tonsillitis, conjunctivitis, inflammation of the middle ear and the accessory sinuses of the nose, pyosalpinx, arthritis, bursitis, tenosynovitis, and abscesses of various parts of the body. Randolph, who examined the conjunctival sac in 48 cases of pneumonia, found practically the same bacterial flora as in health, and suggests that the organisms normally present render the soil uncongenial to other varieties.

Pneumococcus Septicemia.—It is now customary to regard pneumonia as a general pneumococcus infection with the lesion in the lung as but one of the manifestations. Such a view of the disease allows a clearer conception of the clinical symptoms and the complications. That a pneumococcemia, analogous to the similar condition produced in rabbits experimentally, occurs quite constantly is indicated by a very extensive series of investigations of the blood during life. Uniformly successful results were obtained by Prochaska in 50 cases, by Philosofeff-Weber in 56 cases, and by Rosenow in 77 cases. Rosenow's results show that the pneumococcus may be obtained from the blood before any physical signs are evident, thus indicating that the solidification in the lung may be but the secondary localization of a primary blood infection. While the organism is usually obtained at the height of the fever, occasionally successful results have been obtained after the crisis. Pearce, in a study of 118 cases of lobar pneumonia at autopsy,

found the pneumococcus in the heart's blood, liver, spleen or kidney in a little less than one-half of the cases. Morganroth recovered the pneumococcus from the blood of all his cases examined post mortem.

General pneumococcus infection without distinct localization has been reported by Wright and Stokes, Pearce, Flexner, Hektoen, and others as the result of bacteriological examination at autopsy. Persistent and fatal general infection may result even after almost complete resolution of the pneumonic lung.

Numerous attempts to *reproduce lobar pneumonia* in animals have succeeded only recently. By intrabronchial insufflation of pure cultures of pneumococcus in dogs, experimental pneumonia was produced successively in 42 cases with a mortality of at least 16 per cent.[1]

Morbid Anatomy.—It is customary to divide pneumonic solidification of the lung into three stages: engorgement or congestion, red hepatization, and gray hepatization or purulent infiltration.

The lung in the stage of engorgement is deep-red in color, œdematous, and slightly firmer and heavier than normal. From the cut surface a blood-tinged serum exudes. Air is still present, the lung tissue crepitates, though to a less extent than normal, and excised portions float in water. Microscopically, the capillaries of the air cells are seen to be congested, and in the air cells are a few leukocytes, red blood cells, desquamated epithelial cells, small strands of fibrin, and a large amount of serum. This stage lasts but a few hours as a rule, but may persist longer. As patients seldom die in this stage, opportunities for its study are rare.

In the stage of red hepatization the portion of the lung affected is solid, airless, and of a general brownish-red color, relieved only by the carbon depositions in the lymphatics or by the grayish-yellow pleural exudate almost constantly present. The lung is firmer and heavier than normal and its size is equal to that at full inspiration. Not infrequently it shows depressions corresponding to the lines of contact with the ribs. The cut surface is comparatively dry, reddish brown in color, and presents a uniform fine granular appearance due to the protrusion of fibrin plugs from the air cells. From this surface a reddish sticky fluid with fine granular plugs may be scraped. The lung is very friable and may readily be torn. A thick mucus may be present in the large bronchi and fibrinous plugs occlude the smaller.

Microscopically, the alveoli are seen to be filled with a network of fibrin, in the meshes of which are red blood cells, leukocytes, and a few desquamated epithelial cells. A similar exudate may be seen in the terminal bronchi. The walls of the air cells and the supporting tissue about larger vessels and bronchi are œdematous and infiltrated by leukocytes. By proper stains diplococci may be demonstrated in the midst of the exudate. The fibrin at times may be granular or compressed and have a hyaline appearance. It is more abundant at the periphery of the alveolus and not infrequently a mass of fibrin may be seen to extend from one alveolus into another. The bloodvessels, though compressed, are usually pervious; thrombi are occasionally seen. The lymphatics

[1] Lamar and Meltzer, "Experimental Pneumonia by Intrabronchial Insufflation," *Studies from the Rockefeller Institute Reprints*, 1912, vol. xv.

are distended with cells, fibrin, and coagulated serum, and their endothelium shows proliferation. Phagocytic cells may be seen especially in the later periods, as may also lymphoid and plasma cells (Pratt).

In the third stage (gray hepatization) the color changes to a grayish white, the surface is more moist, the granular plugs more prominent. The consistence is the same or slightly less than in the stage of red hepatization. A larger amount of distinctly turbid fluid may be scraped from the surface. As resolution begins the consistence diminishes, the plugs disappear and the surface is bathed in a purulent fluid—a state frequently referred to as a puriform softening. Distinct abscess formation, however, seldom occurs. Microscopically, the air cells are filled with polymorphonuclear leukocytes, the fibrin becomes granular and is obscured by the leukocytic infiltration, and the red corpuscles appear only as shadows.

As resolution, frequently termed the fourth stage, advances, the fibrin and red cells are dissolved, the epithelial cells and leukocytes become fatty, phagocytic cells may become prominent and repair of epithelium evident. The lung becomes softer and gradually assumes its normal appearance. The bulk of the exudate is removed by absorption, resolution being brought about largely by autolysis of the exudate due to a proteolytic enzyme which is much more abundant in the stage of gray than in red hepatization. This enzyme is apparently set free by the leukocytes.

While these several stages are described it is not to be supposed that in all cases they are absolutely distinct. They merge gradually one into the other and not infrequently red and gray hepatization may be seen side by side, while puriform softening in one portion of the lung and early repair in another portion may also occur.

An idea of the distribution of the solidification and of the extent of involvement of the lung may be obtained from the following summary of Osler's Montreal statistics, based on 100 autopsies: "In 51 cases the right lung was affected; in 32 the left; in 17, both organs. In 27 cases the entire lung, with the exception, perhaps, of a narrow margin at the apex and anterior border, was consolidated. In 34 cases, the lower lobe alone was involved; in 13 cases the upper lobe alone. When double, the lower lobes were usually affected together, but in 3 instances the lower lobe of one and the upper lobe of the other were attacked. In 3 cases also both upper lobes were affected. Occasionally the disease involves the greater part of both lungs. In a third of the cases, red and gray hepatization existed together. In 22 instances there was gray hepatization. As a rule, the unaffected portion of the lung is usually congested or œdematous. When the greater portion of a lobe is attacked, the uninvolved part may be in a state of almost gelatinous œdema. The unaffected lung is usually congested, particularly at the posterior part. This, it must be remembered, may be largely due to postmortem subsidence. The uninflamed portions are not always congested and œdematous. The upper lobe may be dry and bloodless when the lower lobe is uniformly consolidated. The average weight of a normal lung is about 600 grams, while that of an inflamed organ may be 1500, 2000, or even 2500 grams."

Accidents of Resolution.—These include organizing pneumonia, abscess, and gangrene.

Organizing Pneumonia.—Very rarely the pneumonic exudate is not absorbed but remains in the air spaces. Under such circumstances the material in each alveolus becomes essentially a foreign body and the surrounding tissues inaugurate other methods for its removal. The process of removal is similar to that which takes place in the canalization of a thrombus or the removal of any necrotic material. The cells of the walls of the alveoli proliferate and new connective-tissue cells in fine protoplasmic processes penetrate the exudate. These processes become canalized, form new bloodvessels, and about them new connective tissue develops, so that eventually the exudate is replaced by a new fibrovascular tissue. This new tissue gradually coalesces with the walls of the alveoli and with the interstitial tissue, so that the involved portion of the lung is eventually transformed into a dense, firm, fibrous, airless mass. Although the exudate has been removed or, rather, replaced, the area of lung affected remains functionless. The condition is termed organizing pneumonia, chronic interstitial pneumonia, induration of the lung or, occasionally, fibrosis of the lung. Under such circumstances the cut surface is reddish brown in color with a smooth glistening surface. It is firm, dense, elastic, and cannot readily be torn. Abundant pleural adhesions are usually present.

Abscess.—This is a rare complication. Laennec found but 5 or 6 cases among several hundred autopsies. Aufrecht found 3 in 253 fatal cases of pneumonia, Musser 2 in 195 cases, Pearce 3 in 121 cases. Grisolle has collected 29 cases, and Tuffier in a study of 49 operative cases found a history of fibrinous pneumonia in 23. The abscesses are usually small, though a cavity 15 cm. in diameter has been described, have an irregular sinuous outline with projecting shreds of tissue and are usually near the surface of the lung. A distinct organizing wall is seldom seen. Indeed, the condition resembles more closely necrosis in an inflamed tissue. The pneumococcus is usually present (Zenker, Pearce), though Cohn found the bacillus of Friedländer in his case.

Gangrene.—Gangrene is also a rare termination. Grisolle in his report of 305 cases of pneumonia does not note this condition and in an analysis of 70 cases of pulmonary gangrene which he collected from the literature, he did not find more than 5 which could be considered as occurring in the course of fibrinous pneumonia. Aufrecht in a study of 1501 cases of pneumonia did not meet with a single case of gangrene. The appearance of gangrene secondary to pneumonia is similar to that occurring under other conditions. Concerning the conditions which determine necrosis little is known. It is assumed that abscess formation usually precedes the putrefactive changes. Microörganisms of putrefaction are of course present and also, as a rule, pyogenic cocci.

Metabolism.—Atwater and Langworthy have studied 27 cases and found that "The assimilation of the nitrogenous constituents of the food in the fever period was in all cases poorer than during convalescence. In the fever period and during two or more days of convalescence an intensified destruction of the protein of the tissues took place. During

the time of convalescence, when the patients began to take sufficient food, a part of the nitrogen of the food was retained. The increased outgo of nitrogen in the urine in the period immediately after the crisis may be chiefly accounted for by the intensified destruction of proteid tissue. The ratio of the extractives to uric acid and urea was higher than normal in all cases in the fever period, and in the majority of cases during convalescence."

Cook studied 22 cases in the endeavor to establish some definite relation between the amount of nitrogen excretion and the rate of absorption of the exudate which might be of practical prognostic value. He concludes that the amount of nitrogen excreted is usually greater than that which would correspond with the amount of the original exudate. He holds that this excess is largely due to a continuation of the formation and absorption of the inflammatory exudate plus other tissue destruction. With delayed resolution the nitrogen output remains high. He believes that this indicates a continued local inflammation, and that such cases are really examples of true chronic pneumonia. When resolution is rapid the leukocyte curve closely simulates the curve of nitrogen excretion, which would seem to indicate that the white corpuscles play an important part in the production of resolution.

There is frequently a great loss of bodily weight in pneumonia. Aufrecht, who weighed his patients on admission, after the crisis, and after discharge, found that individuals ranging in weight from 130 to 150 pounds frequently lost 20 pounds during the course, although this loss was rapidly regained, and at times the original weight was exceeded after convalescence.

Carbon Dioxide Content of the Blood.—A diminution in the carbon dioxide content of the blood is held by Peabody to be a constant feature. Occasional cases, however, may fail to show low carbon dioxide. The carbon dioxide in the blood bears little definite relation to the severity of the disease, except that it tends to be lowest in severe cases and in the terminal stages. There is less deviation from the normal in short or mild cases. The diminution bears no immediate relation to temperature, as it may persist for some days after the patient is afebrile. It corresponds to the other evidences of metabolic changes in infection, and, like them, may be even greater after than during the febrile period. The changes in the carbon dioxide content of the blood run parallel to the output of ammonia in the urine but appear to bear no relation to chlorine excretion. In two unusual cases the carbon dioxide content of the blood was normal or above normal. This was associated with a very low oxygen content of the venous blood.[1]

During pneumonia the *metabolism of inorganic substances* deviates markedly from the normal. While chlorine, sodium, and calcium are retained in the body, potassium and magnesium are excreted normally or in excess. Two cases showed a definite loss of magnesium to the body in the febrile period. During the period of retention the chlorine content of the blood is distinctly lower than normally, the calcium content is

[1] *Journal of Experimental Medicine*, November, 1912, vol. xvi.

apparently slightly lower, and the magnesium content tends also to be a little lower. The skin is shown to play no special part in the chlorine retention. Since no organ or organs have been shown to store up large amounts of the retained substances, it is probable that they are spread diffusely throughout the body.[1]

The *nitrogen and sulphur metabolism* in 19 cases of pneumonia of varying degrees of severity have been examined.[2] The cases of milder type show a smaller loss in nitrogen and sulphur than do those of a more severe grade. The daily loss in nitrogen on a diet adequate to protect a resting individual from nitrogen loss may be from 20 to 25 grams. The relative disamidating capacity, as shown by the ratio of urea nitrogen to total nitrogen, is comparable to that of a normal subject. The capacity for the oxidation of the cystin group, as exhibited by the ratio of total sulphate sulphur to total sulphur, is quite as high if not higher than normal. During the period of hyperpyrexia excessive amounts of creatinin are eliminated. This is followed during convalescence by a subnormal excretion of creatinin. This is taken to indicate the endeavor on the part of the organism to repair the losses sustained during the height of the toxemia.

In the severe cases of pneumonia large amounts of creatin are also excreted. This is seen particularly during the time of greatest nitrogen loss. During convalescence the creatin disappears from the urine. In some of the lethal cases the amount of creatin excreted on the day terminating the illness is as high as the amount of creatinin excreted. During hyperpyrexia, especially in severely toxic cases, unusually high amounts of undetermined nitrogen are excreted. In some cases over 5 grams of nitrogen derived from uninvestigated substances are found in the urine. This nitrogen is not derived from albumoses, as the search for these substances revealed quantities which in no way could account for the large amount of rest nitrogen.

The sulphur excretion runs more or less parallel with that of the nitrogen; but it appears in some of the cases that the katabolism of proteins rich in sulphur is not so marked as those in which the content of sulphur is small. On the other hand, cases progressing unfavorably seem to show an excessive destruction of proteins containing much sulphur. This is made out from the increased ratio of total sulphur to total nitrogen.

Symptoms.—Incubation.—This may be short and in some cases reported by Callender ranged between two and three days. Edsall and Ghriskey's epidemic indicated that it might be less than forty-eight hours. Traumatic pneumonias are extremely interesting in this relation and the time between the injury and the onset is very brief. Some authorities give a much longer interval; Penkert, for instance, places the incubation at from five to eight days.

Prodromes.—In some instances certain prodromes, such as malaise, headache, angina, gastro-intestinal disturbances, etc., may replace or precede the chill.

[1] F. W. Peabody, *Journal of Experimental Medicine*, January 1, 1913.
[2] Wolf and Lambert, *Archives of Internal Medicine*, Chicago, 1910, p. 406.

In a large number of cases the following were encountered, given in order of frequency: chest pain, anorexia, headache, malaise, vomiting, abdominal pain, hemoptysis, delirium, convulsions, somnolence, insomnia, tonsillitis, parotitis, and epistaxis.

Undoubtedly prodromes would be more frequently encountered if their existence were more carefully investigated. Traube, who paid considerable attention to this question, held that such was the case, and further stated that in some instances definite prodromes lasting from several days to weeks occurred. Quite often we find that the patient has had a laryngitis, coryza, or bronchitis, for some time before the onset.

Onset.—An abrupt onset is the rule. Among 1276 cases with exact data 80 per cent. began suddenly and 20 per cent. insidiously. The character of the attack which is to follow is not infrequently suggested by the manner of its beginning. Thus, a rapid onset, with a marked chill, pain in the side and a high temperature, often leads to a sthenic attack, prominent symptoms, sudden termination by crisis, and prompt resolution. On the other hand, a gradual beginning, with vague symptoms, and lower pyrexia, is often followed by a protracted course, defervescence by lysis, lingering consolidation, or untoward sequelæ.

The prodromes are often in no wise characteristic but are those common to a host of infectious fevers. Such symptoms may be referred to practically any organ or part of the body. A certain number of the patients present a mental attitude of apprehension and vague alarm, which is very suggestive.

The stage of invasion, however, is usually very characteristic. Generally a well-marked *rigor* is promptly followed by a rapid *rise in the temperature, cough, pain, and dyspnœa.* The chill is often severe, lasting from one to several hours, the patient feeling very cold, shaking from head to foot, with teeth chattering, cyanosed lips, and icy extremities. Chills are said to be more common during the cold months. Soon the picture changes; the patient recently agonized by frigidity feels overheated; the cheeks are flushed, often more intensely on the side corresponding to the lesion. The pyrexia may be actually not much greater than during the rigor but the patient now becomes conscious of it. The head throbs and feels as if it were bursting; the bedclothes are tossed aside. The skin is suffused with a ruddy glow, feels dry and burning to the touch; thirst appears, the eyes glisten and an expression of anxiety appears. Soon cough and pain increase. The latter, which has been lancinating, and located in the side of the chest, adds to the dyspnœa by restricting the respiratory movements and becomes more intense through continued friction of the inflamed pleural surfaces. In many cases a strong presumptive diagnosis can be made by inspection of the patient and the temperature chart.

The exact relation of the chill to the pulmonary condition is uncertain. Some observers maintain that the disease begins in the lungs and that the chill corresponds to the time at which large doses of toxin are absorbed into the system; others hold that the rigor represents the period at which general systemic infection takes place. Whichever view we are inclined to take, we must explain the production of the prodromes,

particularly chill, vomiting, and convulsions, by the fact that certain irritative substances are carried to the central nervous system, and that these symptoms are referable to a cerebral disturbance (Aufrecht).

The figures of 12,402 cases are as follows: of 9851 cases, 5731, or 58.18 per cent., had a rigor; of 2334 cases, 703, or 30.12 per cent., had chilliness; of 217 cases, 27, or 12.44 per cent., had repeated rigors; of 1705 cases with chill, 366, or 21.47 per cent., died; of 193 cases without chill, 27, or 14 per cent., died. The presence or absence of this symptom appears to depend more or less upon the individual attacked. Thus in the aged and in the subjects of chronic disease chill is less common than in robust adults.

Senile pneumonia begins very insidiously and often without symptoms of any sort until the patient is far gone. In some cases nervous symptoms are predominant, such as severe headache, delirium, mania or convulsions. The last-named are noted most often in children, but it is probable that even in them the frequency of this condition has been very much overrated. A fair proportion of the children who have been subject to convulsions at the time of onset of different infectious fevers develop epilepsy later in life; in other words, the nervous system has been susceptible from the beginning.

Earache on the side of the pneumonia is sometimes of sufficient severity to be for a time the predominant feature. This may occur independently of any local inflammation and disappears within a day or two. There is no discharge, no deafness, and no perforation of the drum. This condition apparently occurs only in children who have had otitis media. It is accompanied by local tenderness.

Pain at the time of onset is extremely common. It usually takes the form of "a stitch in the side," is lancinating in character, agonizing in intensity, and may be limited to the chest or radiate to other regions such as the upper abdomen. Grisolle states that chest pain occurs in 90 per cent. of the cases. It is less severe when the upper lobes are attacked, in central pneumonia, and in children. Among the last-mentioned class, however, there are frequent exceptions.

The pain sometimes occurs on the opposite side of the chest to that affected; very often, however, it corresponds to the site of the consolidation, and frequently a friction rub may be heard either directly beneath or in close proximity to the site of the lesion. It is usually increased by pressure, the patient often complaining bitterly when the region is percussed. On the other hand, firm pressure sufficient to produce immobility, such as is exerted by the entire hand or by the application of adhesive strips, often relieves it. According to Müller it is caused by a lymphangitis of the pleura, due to the invasion of the pneumococcus. Its onset is usually simultaneous with the chill, but at times it precedes or rapidly follows the latter. The duration of the pain is variable. It may disappear within a few hours or last for several days, but it is not usually a prominent feature in the latter days of the attack. It is but little in evidence in most of the senile and asthenic pneumonias and is not noticed by delirious patients at all. Severe pain often, but by no means always, indicates a severe attack of pneumonia. Characteristic of it is the fact that it is greatly

aggravated by talking, breathing, sneezing, and coughing, and that it is greatly ameliorated by immobilization of the chest. Occasionally it is accompanied by cutaneous hyperesthesia. Beside the actual pain, the patient sometimes complains of a vague sensation of oppression and weight in the chest.

Abdominal Pain.—It has happened that patients have been seized with such violent abdominal pain, accompanied by rigidity of the abdominal muscles, that laparotomy has been performed for a supposed appendicitis when the peritoneal cavity proved to be entirely normal, and a subsequently manifested pneumonia turned out to be the cause of the abdominal disturbance. Chatard found abdominal pain 51 times in 658 pneumonia patients (7.7 per cent.). Griffith has reported numerous instances in children, and collected a number from the literature. The possibility of such a condition should therefore always be borne in mind, and if this is done a correct diagnosis can be made in the vast majority of cases. The writer has seen a case of pneumonia associated with severe localized pain over the upper portion of the right rectus abdominalis in which an operation performed in the belief that the trouble was intraperitoneal, disclosed only a hematoma in the muscle itself.

Laennec noticed that the pain of pleuritis was often migratory, and stated that at times "from the onset of the disease we have a stitch on the right side and a pleuritis on the left." Huss explains the occurrence of pain on the opposite side by the anastomosis which at times occurs between the right and left intercostal nerves. Pain at a distance from the seat of the disease is often referred in character, the affected and the painful areas being supplied by filaments from a common nerve trunk. Rohrer considers that abdominal pain is, especially in children, often due to inflammation of the diaphragm itself. Head "believes that in certain cases there may be abdominal pain when the lung is involved without the pleura, *e. g.*, in bronchitis, tuberculosis, or bronchopneumonia."

On the other hand, in a certain number of pneumonia patients we may have to do with actual pathological abdominal conditions as complications, such as acute peritonitis. Griffon and Bezancon have experimentally produced ulceration of the stomach in guinea-pigs as the result of pneumococcus septicemia. Rathery has reported a case of double pneumonia with fatal hemorrhages from the intestine, in which at autopsy the entire colon was spotted with punctiform hemorrhages. Jonnesco has recorded a case in which the intestine showed hemorrhagic foci without ulceration or erosion. Inasmuch as only colon bacilli could be demonstrated in the lesion, the condition seemed to be primarily toxic, with secondary infection. Rose instanced cases of pneumonia in which abdominal pain resulted from local conditions such as intussusception.

The onset of pneumonia is sometimes accompanied by *epistaxis*, which usually occurs in plethoric individuals. *Hemoptysis* has been described by a number of observers. While this symptom should make us suspicious of tuberculous disease yet it sometimes occurs purely as the result of the pneumococcus infection. The hemorrhage may be severe; in one of Hood's patients, the expectorated blood amounted to half a pint and this was repeated several times during the attack. Com-

plete recovery ensued. On the other hand, the investigations of Flick, Ravanel, and Irwin, at the Phipps Institute, Philadelphia, strongly suggest that the pneumococcus plays an important role in the production of hemorrhage in tuberculous individuals.

Hemoptysis occurred in 27 out of 2108 cases collected by the writer (1.3) per cent. The amount of blood lost may be sufficient to seriously influence the course of the disease, but this is extremely rare. Aufrecht has seen but one case of large hemorrhage. Musser encountered the condition twice. Among 16,711 cases of hemoptysis collected by Stricker, only 7 occurred in pneumonia.

Tonsillitis preceded pneumonia in less than 0.5 per cent. of the writer's cases. Cornil succeeded in demonstrating the pneumococcus in the majority of his cases, an experience corroborated by Netter. Landgraf has reported *laryngitis* as a fairly frequent occurrence, which he considered due to excessive coughing, while Fraenkel is inclined to believe that the pneumococcus may have been the etiological factor.

More or less *headache* is usually experienced at the onset; its severity often abates as the attack progresses. It is sometimes a prominent symptom in children, and according to Wells also in the aged, being frontal in such cases. Headache occurred in 17 per cent. of the writer's collected cases. It is at times sufficiently acute to suggest meningitis. *Vertigo* and *syncope* as prodromes are rare.

Convulsions occurred in 1 per cent. of the writer's cases. They are encountered in children, epileptics, neurotic individuals, drunkards, and the insane. According to Kühn, "when they appear in individuals free from nervous troubles they indicate an hereditary neuropathy."

Delirium in pneumonia may arise from various causes: fever, toxemia, inanition, delirium tremens, cyanosis, and meningitis. It is said to be more common when the apices are involved. Among collected cases, 1343 in 7624 had delirium (17 per cent.). In the cases reported by J. McCrae, Fyshe, and Ainley, 90 per cent. of the fatal ones had delirium but only 20 per cent. of the non-fatal, and more than 50 per cent. of the delirious cases, died. In 447 cases, 156 were delirious; of these 93 were alcoholics and 64 non-alcoholics. Heinze reported 317 cases, 98 of these had severe nervous symptoms, of these 40 per cent. were apical, and 25 per cent. basal cases. Delirium is more frequent the more extensive the pulmonary involvement and the more pronounced the toxemia.

The pyrexia may increase but does not necessarily affect the delirium. The character of this symptom varies from slight incoherence to maniacal excitement. In senile and asthenic patients, it is apt to be of the stuporous muttering variety. The onset is often very sudden, and, as delusions are by no means rare, these patients have to be most carefully watched lest they do injury to themselves or to others. Delirium with or after the crisis occurred in 6 out of 239 of Pöhlmann's cases. In 150 cases Elsner found 4 cases of postcritical delirium, coming on from three to ten days after the subsidence of the fever; 3 terminated fatally.

Delirium due to cerebral congestion appears about the fourth or the sixth day, generally lasts only a short time and is attended by a high mortality. It may be of the low muttering or of the delirious maniacal

type. In alcoholics it is apt to persist after the defervescence. Not rarely it is followed by confusional excitement with delusions of persecution or of grandeur; the latter being associated with hallucinations, flights of ideas, and an impulse to constant movement. *Postcritical delirium* generally results from cardiac or vasomotor enfeeblement, with consequent venous stasis and cerebral œdema. This form of delirium occurs chiefly in the debilitated or the debauched. It is associated with great prostration, insomnia, hallucinatory confusion, flights of ideas, and symptoms of collapse. Delusions are usually terrifying in character —persecution, poison, sin—but those of exaltation also occur. The duration varies from a few days to months. About 84 per cent. recover (Krafft-Ebing).

An attack of pneumonia is extremely likely to precipitate delirium tremens in the alcoholic. This follows its usual course and very often ends in death. Of 8998 collected cases, 383 had delirium tremens (4.26 per cent.); among 357 of these, 132, or 36.97 per cent., died. Insanity has been known to follow the delirium of pneumonia.

Insomnia as a prodrome occurs in a small proportion and appears throughout the disease from time to time from manifest causes.

Fever.—The temperature range varies greatly. In sthenic attacks occurring in healthy adults it lies between 102° and 105° F. The higher temperature is favorable, bespeaking a vigorous reaction, as opposed to those instances in which the temperature is only slightly elevated. Apyrexia is encountered chiefly among those who are enfeebled by age, dissipation, or chronic disease; Traube mentions it as occurring in cases complicated by cardiac disease. Ashton and Landis found 9 with subnormal temperature among 991 cases occurring in the almshouse at Philadelphia; all died of uremia. Noica has recorded a case in which during an eight-day attack of pneumonia, in a man aged sixty-four years, both the axillary and the rectal temperatures were persistently more than 3° below normal.

In the majority of cases the fever is of the continuous type. Daily variations occur as in health, but the entire tracing is elevated several degrees above the normal. Occasionally the fever is remittent during the first few days. "Small differences are noted in mild as well as in the severe cases; especially in the latter the average slight remissions alternate not only with the greater ones, but with the intercurrent drops, and these intense, protracted cases not rarely later terminate by lysis" (Aufrecht). Lebert states that an irregular temperature curve is of favorable prognostic import.

Generally the fever rises rapidly, but not always uninterruptedly, immediately after the chill. Jürgensen states that "If women are taken ill with pneumonia during the time at which their menstruation should occur, very high temperatures are usually noted."

Instead of a continuous type of fever, remissions occur during the first few days or irregularly throughout the fastigium. This may be due to infection with other organisms than the pneumococcus. A relapsing type of fever is sometimes seen, a rapid defervescence being followed by an afebrile period lasting a variable number of hours, and terminating

suddenly by a rise to the original height. This secondary elevation may be followed by the final crisis or by a second or even a third pseudocrisis. Accompanying such drops in the temperature there may be no corresponding change in the character of the pulmonary consolidation. Sometimes, however, each recrudescing fastigium is accompanied by the involvement of a new area, being known as wandering or migratory pneumonia. Pseudocrises are in favorable cases followed by the true crisis after a short time.

The crisis is sometimes immediately preceded by an increase of the pyrexia—critical perturbation—it being at the time impossible to determine whether such a rise heralds impending death or a rapid termination of the disease. Very high temperatures are very often fatal, but by no means necessarily so. There are records of hyperpyrexia from 107° to 113° F. followed by recovery. Ironside has reported an instance in which the temperature reached 109° F. on the seventh and 109.5° F. on the fourteenth day of the disease. In the aged and in children the internal temperature may be much higher than it is at the surface; for accuracy therefore measurements should be taken in the rectum.

The duration of the fever in 1987 cases collected by the writer was as follows:

Duration of fever.	Cases.	Per cent.
Two days	4	0.2
Three days	32	1.6
Four days	86	4.3
Five days	195	9.8
Six days	198	10.0
Seven days	346	17.4
Eight days	280	14.1
Nine days	203	10.2
Ten days	183	9.2
Eleven days	96	4.8
Twelve days	81	4.1
Thirteen days	38	1.9
Fourteen days	74	3.8
Fifteen days	28	1.4
Sixteen days	20	1.0
Seventeen days	21	1.1
Eighteen days	37	1.9
Over eighteen days	65	3.3

Pulse.—At the onset the pulse as a rule bears the usual relation to the temperature but falls behind the respiratory rate. It tends to be more rapid in children than in adults, in women than in men, and in persons of small than of large stature. At the beginning of a sthenic attack it is full and bounding, assuming the type which was formerly considered a signal for venesection. Gradually, as the disease progresses, it becomes smaller and weaker. This is particularly the case if much lung tissue is consolidated, the right heart overtaxed, and in patients who are markedly toxic. Sometimes the pulse is much affected by the respiratory movements.

The pulse rate is regarded by many as a reliable prognostic sign; thus Griesinger states that of those with a rate higher than 120, over one-third die. Sears and Larrabee found that the death rate bore a

direct relation to the rapidity of the pulse and the amount of urine voided. Certainly the mortality increases very rapidly when the pulse rate passes 125, a figure which of course does not refer to children, in whom a range of 120 to 200 is not so very rare. But we must not place our estimation upon the rapidity alone; the rhythm, volume, and tension are of even greater importance. Any deviations from the normal in respect to the character of the pulse call for the most careful attention; and, as a general rule, the earlier in the course of the disease they appear, the less favorable is the outlook. "In all cases of acute lobar pneumonia that I have met, when the pulse showed even an occasional irregularity before the crisis was reached, death supervened. In pneumonia the amount of arterial pressure, the rate of the pulse, and its rhythm, are each of them among the most important indications we possess. Within a few hours after a rigor the fatal termination may be too plainly foretold by the character of the pulse. I have rarely seen an adult with a pulse over 140 recover" (Mackenzie).

There can be no doubt that if the pulse were studied routinely with a clinical polygraph, and if the results thus obtained were interpreted not in their own light alone but in correlation to the data concerning the blood pressure, we should have much more accurate and satisfactory knowledge (see Arrhythmia).

The normal relation of the respiration to the pulse is 1 to 4.5; in pneumonia it may be 1 to 3, 1 to 2, or even 1 to 1. In doubtful cases, with equivocal physical signs, such a disturbance of the ratio is often very suggestive of this disease. The postcritical pulse is slow unless cardiac weakness is very great; in some cases an actual bradycardia is encountered.

Blood Pressure.—There is considerable daily variation in the blood pressure, although the general tendency of the infection is to cause a fall. "When one pictures the possible causes for variation in lobar pneumonia, the difference in individual reaction to toxemia, in extent of lung tissue involved, the motor restlessness of some patients, the urgent dyspnœa of others, and the great likelihood of an asphyxial rise of pressure when cyanosis is extreme, there is little wonder at the somewhat discordant results" (Janeway.) Blood pressure readings should be made in all cases routinely so that proper treatment in case of vasomotor paresis may be instituted early. Patients in whom the pulse rate per minute exceeds the blood pressure in millimeters of mercury are in danger (Hare).

The Heart.—Examination of the heart itself, aside from the rate, may reveal nothing abnormal, but very often, especially during the latter part of the attack, we find functional murmurs either with or without dilatation. In this latter condition the right side is the greater sufferer by reason of the obstruction to the pulmonary circulation. The mere fact, however, that the area of dulness extends beyond the right sternal border need occasion no alarm unless there be other evidences of cardiac weakness, as this may be produced by retraction of the lung. According to Jürgensen, it occurs as the result of shallow breathing, which, owing to lessened inflation of the lung, imposes less counter force to the elastic tissue, thus permitting the elastica to retract the overlapping pulmonary

margins. A second cause for apparent dilatation may arise from consolidation of the left lung, which tends to displace the heart to the right and a similar result may be caused by a left-sided pleural effusion. If the right middle lobe is infiltrated it may be almost impossible to outline the right cardiac border. In some severe and fatal cases no cardiac dilatation may be demonstrable.

Functional murmurs are common; they may arise from relaxation of the myocardium, from the rigidity imposed upon the large vessels at the base by consolidation of the surrounding lung tissue, or from changes in the composition of the blood. Organic murmurs may result from preëxisting valvular disease or from acute endocarditis; the possibility of the latter should always be borne in mind. Of great importance is the character of the second sounds at the base. The *pulmonic sound* is generally accentuated, sometimes reduplicated. The disappearance of an accentuation is often a sign of ominous import, pointing to the fact that the overburdened right heart is giving way and an acute dilatation impending. When the upper lobes are the seat of the disease, the character of the second sound is less reliable, for the reason that a neighboring consolidation may cause a weak sound to seem clear and intense. As in other forms of pulmonary infiltration, the heart sounds are often transmitted very distinctly to distant parts of the chest.

Cardiac weakness in pneumonia may arise from a number of causes; the commonest and most important of these are toxemia, extensive pulmonary consolidation, and hyperpyrexia. The first of these may result either from a direct action of the poison upon the muscle itself—cloudy swelling, myocarditis—or indirectly through vasomotor paresis.

Sudden syncope may occur at any time in the course, although this is rare, occurring according to Aufrecht in about 0.5 per cent. The pulse is rapid and small in volume, and the attacks, even in patients who recover, may last six or even twelve hours. The usual symptoms of heart weakness, including cyanosis, dyspnœa, cold extremities, and nervous derangements, occur. Critical collapse, or at least a tendency toward it, is quite common. It sometimes appears at the beginning of the crisis, more rarely in the midst of it. It is accompanied by chilliness, cold perspiration, dyspnœa, cyanosis, a weak rapid irregular pulse, mental incoherence and subnormal temperature. With judicious stimulation these attacks are usually passed in safety, although death in the course of them is by no means unknown. Collapse coming on a day or two after the crisis is much more grave, being usually an indication that the myocardium has sustained serious damage. It sometimes happens that the patient falls back dead, after sitting up, although there had been no indications of danger. In such cases one naturally thinks of an acute cardiac dilatation or a pulmonary thrombosis as the cause of death.

Respiration.—The character of the breathing is very significant, often absolutely diagnostic. The respirations are short, shallow, voluntarily and involuntarily restricted, and accompanied by movements of the alæ nasi. Later on as pain diminishes the involvement becomes more extensive, they increase in depth, become more labored and the accessory muscles are called into action. The rapidity is due in part to the pain

and fever, in part to the amount of lung involvement, and in part to the toxemia or cyanosis. Washburn has shown that mice infected with the pneumococcus are dyspnœic although pulmonary consolidation is absent. Owing to the pain the respirations are not sufficiently deep. The truth of this is shown by the fact that an injection of morphine which allays the pain will often cause the disappearance of the cyanosis and an alleviation of the dyspnœa. The causes mentioned contribute to increase the respiratory rate far beyond the normal, in relation to the pulse and temperature, and this may persist after the crisis, when the last named have fallen to normal or below it.

The gravity of the respiratory condition is not to be reckoned by the rate alone. Thus, when pain is a prominent feature, the breathing may be very rapid, and yet the patient is in much less danger than when the actual count is lower with cyanosis, distended jugular veins, and cold extremities present. The "expiratory grunt" is a sign of great diagnostic importance, especially in children. It may occur although pain be absent.

The rate in adults usually ranges between 24 and 48 per minute; only 11 per cent. of Gerhardt's cases had respirations over 40 per minute. While an exact danger line is hard to draw, respirations of 50 or more, unless due to some definite cause such as great pain, mental excitement, pleural effusion, etc., are usually a cause for apprehension, especially with lividity and marked movements of the alæ nasi. Respirations of 90 to the minute have been recorded. Jürgensen has, in severe cases of arteriosclerosis, seen the respirations more rapid than the pulse. In children the range is generally between 40 and 50. Musser saw a child aged two and one-half years, with pneumonia, breathing 120 times to the minute.

Dyspnœa.—Dyspnœa, one of the commonest symptoms of pneumonia, is generally explained by the lessened respiratory area in the lungs and the restricted movement which results from pleuritic pain. It is not, however, present in proportion to the extent of pulmonary involvement, since it is brought about not only mechanically but also as the result of toxemia. As a general rule, if the dyspnœa is greater than can be accounted for by the extent of the lesion the prognosis is bad, excepting of course those cases in which the shallow and rapid respirations are due to great pain as when the diaphragmatic pleura is involved.

Cyanosis.—Cyanosis is generally a late symptom which bears a more or less constant relation to the extent of the pulmonary consolidation and to circulatory stagnation. Early cyanosis is prognostically unfavorable, and is generally met with in the asthenic type of the disease such as occurs in seniles, alcoholics, cardiac cases, and in terminal infections. Cyanosis is also a prominent symptom in cases of pneumonia complicated by thyroiditis, mediastinitis, endocarditis, pericarditis, and pregnancy, as well as in the secondary pneumonias following carbon monoxide poisoning and the aspiration of foreign bodies (v. Neusser). Dyspnœa and cyanosis often herald the occurrence of right-sided cardiac dilatation and appear coincidently with a weakening of the pulmonic second sound. Cyanosis may also result from the administration of coal-tar products or other circulatory depressants, from œdema of the lungs, thrombosis

of the pulmonary veins or cardiac paralysis. Cyanosis of sufficient extent to be clinically recorded occurred in about 10 per cent. of the collected cases (119 among 1239).

Cough.—Cough is nearly always present, the exceptions usually being in the aged, in those with delirium tremens, in apical lesions, and in the pneumonias secondary to circulatory disease, typhoid fever, and puerperal sepsis. Jürgensen very aptly remarks that "it is rarely useful, always troublesome, sometimes dangerous." It appears early in the course, usually with or soon after the chill. It precedes the latter symptom when bronchitis antecedes the pneumonia. At first it is unproductive, paroxysmal, and extremely painful. Later on, expectoration appears and the cough may partially abate; often, however, the paroxysms increase in severity and duration as the attack progresses, severely taxing the patient's strength by preventing sleep, his nervous system by excruciating pain, his right heart by increased pressure, and his respiration by muscular stiffness and fatigue. The sudden disappearance of cough is an unfavorable symptom, not rarely heralding the onset of exhaustion, stupor or coma.

Sputum.—The sputum is at first scanty, frothy, white or faintly streaked with blood, and may contain diplococci. In the course of a few hours it becomes rusty or brick-dust in color, as the result of an increased admixture with blood; it is uniformly mixed throughout a glairy menstruum which is viscid and tenacious. Microscopically many crenated red blood corpuscles are seen; the color is due in part to these and in part to dissolved hemoglobin. To the naked eye it has a vitreous, glairy, semitranslucent appearance. Later, leukocytes and shreds of fibrin cause it to become opaque. Casts of the bronchioles and Curschmann spirals are also encountered. Sometimes a green color is met with either in the early or late stages of the disease, a condition which Nothnagel considered due to changed bile pigment. According to v. Jaksch, hemoglobin and bilirubin are changed to biliverdin in the lungs. On the other hand the green hue may, as Rosenbach has pointed out, be produced by microörganisms such as the *Micrococcus chlorinatus*. In the course of time the sputum becomes less viscid and more profuse, the color changing from a pink to a citron yellow or saffron; gradually erythrocytes and leukocytes decrease, as do also the color and the amount of the alveolar epithelium; changes which become more pronounced during the stage of resolution. Occasionally the sputum continues blood-tinged throughout the attack. According to Osler it ranges from 150 to 300 cc. daily. Only a small part of the inflammatory exudate of the lungs is coughed up, the greater part being absorbed.

During the febrile stage the sputum contains large numbers of microorganisms, which rapidly decrease in number after the crisis. The duration of the attack can at times be forecast to a certain extent by the nature of the organisms found; thus a pneumonia due to the influenza bacillus, or in which there is mixed infection, runs a more protracted course and instead of terminating by crisis, does so by lysis, and is more apt to be followed by delayed resolution, suppuration, gangrene, or other abnormality. The identification of the pneumococcus in the sputum is

usually easy and should be attempted routinely. The tubercle bacillus is to be sought for in suspicious cases. The number of pneumococci in the sputum does not bear any constant relation to the severity of the attack. Stuertz has made a study of the virulence of the organisms in the expectoration by injecting mice and has shown that the crisis is not due to decrease in the virulence. Exacerbations and relapses, however, are accompanied by increased virulence.

The sputum is sometimes very hemorrhagic. This has been observed in tuberculous cases (Walshe), in heart disease (Huss), in lobar pneumonia produced by the typhoid bacillus, in traumatic pneumonia and if infarction has occurred. Leichtenstern suggested that atheroma of the pulmonary artery may cause the so-called "hemorrhagic pneumonia." In Grisolle's 131 cases rusty sputum appeared within the first two days in 60 per cent.

Among collected statistics: of 3286 cases, 1627, or 49.51 per cent., had rusty sputum; of 1406 cases, 203, or 14.44 per cent., had mucopurulent sputum; of 5249 cases, 70, or 1.33 per cent., had bloody discharge or free hemorrhage; of 25 cases, 19, or 76 per cent., had casts of air vesicles; of 2184 cases, 361, or 16.53 per cent., had no sputum. Hemorrhagic infarction of the lung gives a sputum similar to lobar pneumonia but even here the expectoration is more bloody, less viscid, and lacks the bright red color. "Prune-juice" sputum has been attributed to lessened coagulability of the blood and a diminution of cardiac power, having therefore been regarded as an unfavorable symptom which sometimes precedes an œdema of the lungs. Williamson states that pneumonia due to the Friedländer organism is to be suspected when the mucus is "intensely mucoid, ropy, and stringy, so that when lifted on a knife-blade or similar instrument it can be drawn into long threads. This is not remarkable when we remember the peculiarity of the Friedländer organism in the culture media." When jaundice is present the sputum may be bile-stained and have a bitter taste. Sometimes expectoration is entirely absent. This occurs notably in children who swallow it, and in delirious or stuporous patients, who fail to cough it up. It is decreased in pneumonia affecting the upper lobes.

As to the *chemical composition of the sputum*, all investigators are agreed that the albumin content is high, owing mainly to the large amount of blood which it contains. After the crisis the amount of albumin is markedly decreased. Bussenius was able to demonstrate glucose in the expectoration of a diabetic woman who had developed pneumonia. "The basis of the pneumonic expectoration is water, albumin, mucus, fat, and salts, with which the other more adventitious elements are mixed. The expectoration is usually neutral or slightly alkaline, rarely acid" (Wells).

Falk and Tedesko have claimed that salicylic acid and its salts after administration by the mouth will appear in the sputum in conditions associated with pulmonary involvement, and will thus differentiate the latter condition from simple bronchial affections. These claims have not been supported by Armstrong and Goodman, who conclude that salicylic acid is excreted if at all in such small amounts as to make it useless in the diagnosis of pulmonary conditions. Armstrong and

Goodman also tested the sputum of patients who had received hexamethylenamine, but found it excreted in the sputum of bronchitis and asthma as well as in that of tuberculosis and pneumonia. Diagnostic value has also been attributed by Wanner, Roger and Levy-Valenski, and others to the finding of albumin in the sputum, but Goodman in cases of bronchitis and asthma as well as in cases of pneumonia and tuberculosis, found not only albumin and albumose, but also occult blood and red blood cells.

The demonstration of Fraenkel's pneumococci in the sputum of patients suspected of having pneumonia though not as positive as the evidence derived from a blood culture may be considered satisfactory evidence that such is the case; particularly if they are found in large numbers and in the central parts of washed sputum.

Method.—The sputum for examination should be collected in a regular sputum cup, or in a wide-necked bottle, and when possible a liberal quantity obtained. Neither water nor disinfectants should be added. A smear is made in the usual manner by rubbing the sputum for a time between two cover-glasses. The diplococcus of pneumonia stains well with Gabbett's methylene-blue solution, but its characteristic biscuit-shaped contour is better brought out by Bismarck brown. When thus stained each coccus is seen to be surrounded by a narrow hyaline space, bounded by a faint marginal capsule. Encapsulated pneumococci are seen with difficulty. The staining of the capsule is best accomplished by the following method: The smear is placed in a 1 per cent. solution of acetic acid for one or two minutes. The excess of the acid is then removed with a pipette and the slide dried in air. After this it is placed for a few seconds in saturated aniline water and when dry examined. The microscope reveals elongated lance-shaped cocci, generally arranged in pairs, with their bases approximated, and characteristically encapsulated. E. C. Rosenow[1] gives a method of staining by which the pneumococci appear stained a deep brownish black and the capsules pink.

If desired, the double-staining method of Wolf may be employed. The dry smear is stained in aniline water saturated with fuchsin, and then placed for one or two minutes in a diluted aqueous solution of methylene blue. The cocci are thus stained blue, the capsule rose color, and the body of the preparation a bluish red. The Friedländer pneumobacillus may be stained by the same methods as the pneumococcus and also shows capsule formation. As indicative of pneumonia Bittorf states that the sputum possesses *no ferments*, as does sputum containing an equal number of leukocytes in other diseases. Rosenow[2] found a much larger number of viable pneumococci in the consolidated areas during the later stages of the disease in fatal than in non-fatal cases.

Posture.—The posture assumed by the pneumonia patient varies. Most often the dorsal decubitus is chosen and the affected side is usually avoided on account of pain and tenderness; the sitting posture is rarely assumed except in case of apical involvement, in which the lateral

[1] *Journal of the American Medical Association*, 1911, lvi, p. 418.
[2] *Journal of Infectious Diseases*, 1911, vol. viii, p: 501.

position is also occasionally adopted. The reason of this is that in basal lesions the movements of the heart, the diaphragm, and the lungs themselves, are least encroached upon when the consolidated portion falls back against the posterior thoracic wall.

Perspiration.—This may occur at any time during the attack. It is most common during or after the crisis, more frequently seen in children and in young adults, and in uncomplicated, sthenic cases; occasionally it is very profuse. Sweating also occurs during the last few hours in fatal cases as the result of vasomotor paralysis. Sudamina may occur upon the reappearance of sweating after its absence during the height of the disease.

Herpes.—This is a very common and often diagnostically significant symptom. It generally appears upon the lips, or at the angles of the mouth or nose, but may be about the ears, eyes, chin, anus, genitalia, legs, or in fact any part of the body. The vesicles may appear with the prodromes. Aufrecht mentions an instance in which they preceded the pneumonia by two days. Generally, however, they appear about the third day of the disease. The eruption of the vesicles may be preceded by a chill, but this is by no means always the case. The condition is easily overlooked because in some cases only a single vesicle appears. The number may range to many dozen. Often they are overlooked because they appear just within the nose. These facts probably account in some measure for the great discrepancy in reports as to their frequency, although there is no doubt that they are more common in certain years and epidemics.

It was formerly supposed that herpes arose as the result of a disordered condition of the blood, but the very interesting investigations of Howard[1] seem to have definitely established the etiological factor to be a neural one located in the nerve, skin, and posterior spinal ganglion corresponding to the nerve in the distribution of which the eruption appeared. When they appear in the distribution of the fifth nerve, the lesion is in the Gasserian ganglion. The pathological changes consist of congestion, hemorrhage, cellular infiltration, degeneration of the ganglion cells, and are probably the result of the toxins.

Since the appearance of Geissler's article it has been believed by many that the appearance of herpes was a favorable prognostic sign. This contention is supported by the majority of available statistics. Among the writer's collected cases, 943 out of 4447 had herpes (21.21 per cent.). The site of the pulmonary lesion bears no constant relation to the location of herpes.

Urine.—This is decreased in quantity, abnormally concentrated, being therefore "high colored," increased in specific gravity, and often irritating. The latter quality may be manifested by burning pain on or after micturition; and in women with perineal lacerations in whom coughing and weakness may produce incontinence, excoriation of the skin. The quantity voided is about one-half the normal, remaining at this level while the fever lasts. Entire suppression is rare. The author

[1] *American Journal of the Medical Sciences*, 1903, cxxv, p. 256.

saw a middle-aged man with pneumonia, the right upper and middle lobes being involved, in whom there was absolute anuria for one day during the febrile period. Beyond somnolence, there were no symptoms of uremia. Crisis with perfect recovery followed. Epicritical polyuria is sometimes seen. The darkened color is due in part to concentration, and in part to increased urobilin, resulting from the destruction of erythrocytes. Uric acid and urea are increased. The urea is increased after the crisis, according to Scheube: (1) because the disintegration of albumin probably continues for a time after the pyrexia; (2) increased diuresis tends to flush accumulated urea from the system; (3) resorption of the pulmonary exudate produces increased albuminous material which is mainly eliminated by the kidneys. Pick has called attention to the fact that in some cases the acidity of the urine may be decreased even to the point of actual alkalinity immediately after the crisis.

The *chloride excretion* is greatly diminished, and quite often entirely suppressed. This lowered excretion is of no prognostic value and is of diagnostic aid only in so far that it occurs more constantly and to a greater extent in pneumonia than in other conditions. (See under "treatment" sodium chloride.) The urinary excretion of iron, according to Goodman, follows a distinct curve, there being hyposiduria during the height of the infection, and a relative hypersiduria (in most cases an absolute hypersiduria) at the time of the crisis or during the day following.

As in other febrile disorders, *albuminuria* is common in pneumonia. This is considered under the renal complications. Among the abnormal substances in the urine we have, as in other fevers, an increase in acetone. Von Jaksch has shown that this is also found in the expired air in some cases. The diazo reaction is more common than in other fevers, but less so than in typhoid fever. It has no practical significance. Among collected cases, 35 in 366 gave this reaction (0.95 per cent.). Indican was found in 10 of 366 (0.27 per cent.).

As regards *cryoscopy*, F. E. Schmidt has found that (1) the freezing point of the urine is considerably lowered and (2) to a greater extent than the concentration of the urine can account for; (3) the lowered freezing point is not due to abnormality of the chloride constituent but to metabolic molecules excreted.

The Spleen.—As in other infectious fevers, enlargement of the spleen occurs in pneumonia. This was first pointed out by Friedreich, who found "considerable swelling of the spleen during the first few days," which later "developed to such an extent that it protruded below the costal arch, and could be clearly palpated," being about as large as the splenic enlargement of typhoid fever, from which, however, it is distinguished by the fact that it assumes the normal dimensions as soon as the fever disappears. This form of splenic enlargement is due to hyperplastic swelling of the parenchyma and usually appears before consolidation of the lungs is far advanced. Clinically demonstrable splenic enlargement occurs more often in fatal than in non-fatal cases.

Adenitis is also encountered; Manchen found enlargement of the lymph nodes quite frequently. It was found in nearly one-fourth of the cases

at the Würzburg clinic, occurring 77 times in 259 cases, with the following distribution: inguinal 36, cervical 14, and both 13.

The Blood.—During the febrile period the red cells and hemoglobin are practically normal. There is often a slight post-febrile anemia, chlorotic in type.

In the large majority of cases there is a marked increase in the number of leukocytes, but cases occur in which there is no increase, and these are not infrequently fatal. Of 108 collected cases of pneumonia in which leukocytosis did not occur, 94 resulted fatally. In children the leukocytosis may be very marked. According to Cabot, when either the patient or the disease easily gains the upper hand there is no leukocytosis, or only a slight one; but in the much larger class of cases in which the struggle is a fierce one, leukocytosis appears, whichever way the battle results. When the patient is already ill from some other morbid process such as typhoid fever, variola, alcoholism, or chronic disease, there is no increase in the white cells. In these cases the absence of leukocytosis is not necessarily an unfavorable sign.

Leukocytosis generally appears soon after the chill, sometimes with it, and probably reaches its maximum within a short time. There may be a slight rise in the number of leukocytes during the period of the decline of temperature. The temperature curve reaches normal before the leukocyte curve. The latter takes from one to three days longer to reach the normal, but may be delayed for some days, even though the lungs are resolving. In delayed resolution the leukocytes remain elevated after the temperature has reached normal and may not fall for some weeks. There is no correspondence between the temperature and the leukocyte curve according to Gaitskell. In the majority of cases the leukocytes reach their normal number before the disappearance of abnormal physical signs. In delayed resolution, however, the abnormal signs clear up at about the same time that the leukocytes reach normal. The polymorphonuclear cells are enormously increased both absolutely and relatively during the febrile period, often making 80 per cent. of the white corpuscles. There is a slight drop in their number during the crisis. On the day after the crisis there is a further lowering of their percentage. After the leukocyte and temperature curves have reached normal, the polynuclear cells continue to diminish until they are exceeded in number even by the lymphocytes. These latter vary inversely in percentage with the polynuclears. As the polynuclears increase, the lymphocytes diminish in number, and *vice versa*. The large mononuclear and transitional cells follow an irregular course. The eosinophiles are rarely present during the fever. They may appear during the crisis, but more commonly after it. They are present during delayed resolution.

Myelocytes are present during some stage of the disease and may reach 11 per cent. They may precede the crisis or occur during it. They are found present on the day after the crisis and their numbers are comparatively large after the temperature has fallen. In delayed resolution they are present in small number. They may be present without eosinophiles. The mast cells are rarely unassociated with eosinophiles. They appear during one of the first three days following the crisis. The blood

plates are greatly increased after the crisis. Iodophilia is present in practically all cases. Dunn has noticed that it persists in cases of delayed resolution, whereas in normal cases it disappears a day or two after the crisis. According to Bernicot, the absence of iodophilia is a sign of great negative value in cases of suspected delayed resolution or abscess.

Leukolysis.—In no other disease, with the possible exception of cancerous cachexia, is there so great a destruction of leukocytes in the blood. . . . These changes are more marked in the more severe cases (Gulland and Goodall).

Regarding the diagnostic value of the leukocytes Cabot makes the following statements: In central pneumonia marked leukocytosis excludes malaria, typhoid fever, uncomplicated influenza, tuberculosis, and scarlatina if suppuration can be excluded. In capillary bronchitis we find a leukocytosis, so that no inferences can be drawn as to the presence or absence of pneumonia. In the pneumonia of children and the aged a leukocytosis often directs our attention to the lungs. The determination of *Arneth's* blood picture was found to be of no clinical value in the cases of pneumonia studied by Miller and Reed. Both diagnostically and prognostically the leukocytosis, the differential count, and the glycogen reaction may be of material assistance.

Cabot studied the leukocytes in 186 cases with the following results: 24 cases had 10,000 to 15,000, 48 had 15,000 to 20,000, 46 had 20,000 to 25,000, 19 had 25,000 to 30,000, 4 had 30,000 to 35,000, 7 had 35,000 to 40,000, 2 had 45,000 to 50,000 and 4 had 50,000 to 55,000.

The finding of pneumococci in the blood is of no prognostic import, being largely a question of technique.

Coagulation Time.—The coagulation time of the blood was found by Dochez to be generally prolonged during the acute stage of lobar pneumonia, returning to normal during the period of convalescence. There seems to be a simultaneous increase in the quantity of circulating fibrinogen. The lengthening of the coagulation time is probably due to an increased formation of antithrombin. The source of the increased antithrombin and fibrinogen is probably the liver, and the stimulus to increased production of these two substances is due to the nature of the infecting organism.[1] Ewart, on the other hand, found that coagulation time decreased until the time of the crisis, and that a coagulation time of less than one minute betokened a fatal outcome. In cases of empyema he found a lengthening of the coagulation time at the time of and after the crisis, followed by a second period of shortening.[2] The *blood platelets* are always diminished in number up to the time of the crisis, after which they are more abundant than normal.

Clinical Varieties.—In addition to the usual type of pneumonia a number of special varieties occur from time to time, which have come to be regarded as more or less definite clinical entities, although some of these are due to organisms other than the pneumococcus and some probably result from mixed infection.

[1] *Journal of Experimental Medicine*, 1912, vol. xvi, No. 5.
[2] Ewart, quoted Gulland and Goodall, "The Blood," 1912.

Wandering or Migratory Pneumonia.—This is a form of the disease which tends to spread from one part of the lung to another, resolving in one part while it spreads in another, in much the same way as erysipelas. There are two distinct types, one in which the inflammatory process travels by direct continuity or contiguity to neighboring parts, the other in which the disease affects different regions of the same or different lobes as time goes on. The latter variety was called "erratic pneumonia" by Wunderlich, and occurs especially in influenza pneumonia. Migratory pneumonia is simply an exaggeration of what occurs ordinarily in many typical cases, in which, if carefully watched one can often observe small areas giving evidences of resolution, while the consolidation tends to spread in another direction. It is sometimes difficult to draw a distinction between wandering pneumonia and recurring pneumonia. Homburger and Ruge have called attention to the tendency of this form of pneumonia to run a protracted course. Migratory pneumonia occurred in 8 out of 813 collected cases (0.98 per cent.).

Asthenic or Senile Pneumonia.—This is a term used to designate the disease as it occurs in senile patients and in those enfeebled by chronic illness or cachexia. It is characterized especially by a gradual insidious onset, often without chill or any prodromal symptoms; in fact, in bedridden patients its presence may be unnoticed until it is far advanced, and occasionaly it happens that the disease is unexpectedly revealed at autopsy. In other cases we suspect a pneumonia on account of the patient's weakness, respiratory rate, fever, or other symptoms, and yet the most careful examination may fail to reveal any definite physical signs until two or three days later. In such case the inflammatory process may begin in the central parts of the lung, and only gradually make its way to the periphery. Charcot refers to lobar pneumonia as "that great enemy of old people, and one of the principal causes of death at the Salpêtrière."

This variety is often located at the apex of the lung and frequently accompanied by severe nervous symptoms, such as delirium and coma. Prostration is nearly always profound. Gastro-intestinal symptoms such as vomiting and diarrhœa may predominate. Cough and expectoration may be absent; dyspnœa is usually not great although the respiratory rate be high, and cardiac weakness is very evident. The temperature may be normal or subnormal and is hardly ever high. The course is a protracted one; when recovery occurs the fever defervesces by lysis and convalescence is slow. Leichtenstern states that complete consolidation of lung tissue is unusual, the stage of red hepatization is short, and the tendency to terminate in abscess or gangrene of the lung quite marked.

Apical Pneumonia.—This has long been believed to possess definite clinical features; thus, delirium and hyperpyrexia are said to be more common. Opinion seems to differ as to the mortality. Apical pneumonia is supposed to be more common in children and in the aged. The general mortality is the same as in other locations, but if uncomplicated in children this is almost *nil*. Delirium in these cases is not an unfavorable prognostic symptom at any age. Flushing of the cheek on the affected side owing to irritation of the cervical sympathetic is more common than

in basal lesions. Pericarditis is also said to be a more frequent complication. The right apex is affected about twice as often as the left.

Central Pneumonia.—This is usually simply an incomplete consolidation which has begun in the deeper parts of the lung. This view is held by many authorities and has apparently been substantiated by means of the *x*-rays. From such studies it appears that as a rule all cases of pneumonic consolidation begin about the hilus of the lung (see under *x*-ray examination).

Synonymous with central pneumonia is the variety which is spoken of as "*latent* or *larval*." This occurs in the asthenic forms, chiefly among the aged and enfeebled, frequently as a terminal infection. As the name implies, the disease manifests itself neither by symptoms nor physical signs, but generally some signs could have been elicited by careful examination. Often these cases are discovered only at autopsy.

Terminal Pneumonia.—This occurs frequently, especially during the winter months, in patients with debility and chronic disease, such as cardiovascular, renal, or pulmonary. Alcohol is an important factor in its development. There may be little or no elevation of temperature or pulse, and death is often impending before the condition is recognized. Despite the paucity of physical signs, extensive consolidation may be found at autopsy. Among 658 cases of lobar pneumonia at the Johns Hopkins Hospital 35 cases of terminal pneumonia occurred. Among 81 of the autopsies in pneumonia collected by the author, 12 were terminal infections.

Abortive Pneumonias.—These run their course in a short time, the duration varying from one to three days. They are unusual, and when they occur consolidation has usually been incomplete. Dusch reported 9 such cases among 173, none of them being fatal. The possibility of a "one-day pneumonia" is denied by many physicians, but there is much clinical evidence to prove that such a condition does occasionally occur. Bechtold[1] found 10 cases belonging to this category among 1057 cases of pneumonia at the Würzburg clinic. Chill, high fever, and crisis were observed in all of them, but the findings on percussion and auscultation differed greatly.

The clearer conception of pneumococcus infections renders such attacks much more comprehensible. We know that a pneumococcemia may exist without symptoms and also that the symptoms of pneumonia depend more on toxemia that upon the extent of pulmonary involvement.

Postoperative Pneumonia.—Much diversity of opinion exists regarding postoperative pneumonia. In every large hospital from time to time pneumonia occurs among surgical patients shortly after etherization. That anesthetics and operations may not infrequently be unjustly blamed is shown by such cases as have been reported by Gould and Da Costa, in which unsuspected pneumonia was accidently discovered just before etherization. A number of theories have been advanced to account for the condition. The possibility of hematogenous infection has received considerable attention, but the consensus of opinion seems

[1] *Münch med. Woch.*, 1905, vol. lii, No. 44.

to be that the infection comes by way of the air passsages. Pulmonary infection through small emboli, hypostatic congestion, infection through the diaphragm, especially in gall-bladder cases, the entrance of infected air into the abdominal cavity when the peritoneum is opened, have all been offered as possible explanations by different observers. Graves believes that postoperative lung conditions occur somewhat more frequently and are more fatal in patients previously septic or desperately ill, or in the aged and feeble. Richy's figures indicate that clean cases are nearly as liable to pulmonary complications as the septic but are more atypical and less severe while the mortality is almost *nil.* The influence of trauma is also important.

Postoperative pneumonia was known before the days of anesthetics and may follow an operation under local anesthesia. Just how much the administration of ether has to do with the production of the disease is uncertain. Silk found 13 cases in 5000 operative anesthesias, 8 of which occurred in tongue or jaw cases. Von Beck states that owing to the injurious after-effects upon the respiratory tract the use of ether has been largely restricted at Czerny's clinic. Anders found that pneumonia was more common after gynecological operations than in the general surgical clinics. The greatest number of cases occur in the winter months. Postoperative pneumonias are sometimes lobular in character.

Among 1196 laparotomies at Munich, Gebele found disease of the lung following in 77, or 6.43 per cent. Of these, 53 died—20 from hypostatic congestion, 8 from "ether" pneumonia, 26 from "aspiration" pneumonia, and 14 from embolic pneumonia. Of the latter, 8 occurred with, and 6 without, peritonitis. Gebele performed 40 celiotomies in rabbits, and found that pulmonary emboli occurred in 12 and pneumonia followed in 4. These conditions appeared both in septic and in aseptic operations. It seems, therefore, as if the pneumonia was due to an embolus plus bacteria, which latter may exist in the lung beforehand or be carried there by the embolus.

Among a collected series of 139,101 cases of anesthesia, pneumonia occurred in 499 (0.35 per cent.). The most generally accepted predisposing factors of this variety of pneumonia are: chilling of the patient by evaporation of ether or exposure of the body, retained or aspirated secretions, and direct infection from non-sterilized inhalers. It is probable that several of these causes may be active in a given case; but the pneumonia may be independent of these and simply coincident.

Repeated and thorough cleansing of the nose, throat, teeth, and mouth before operation is to be recommended. Risley advises using the Trendelenburg position in all prolonged abdominal operations when practical and when gravitation of septic material toward the diaphragm can be prevented.

Pneumonia in Childhood.—Croupous pneumonia in children often follows a very different course than in adults. A chill may usher in the attack, but quite frequently this is replaced by gastro-intestinal symptoms such as nausea and vomiting, or by nervous derangements, such as convulsions, delirium, drowsiness or stupor. Hence, we may be misled into supposing that we have to deal with typhoid fever or

meningitis. Other cases begin with sore throat, tonsillitis, and erythematous flushing of the skin, thus simulating scarlet fever. Fever is practically always present and frequently high. Careful observation of the manner and frequency of the respirations is of the greatest importance. Movements of the alæ nasi may or may not be present. Among 270 pneumonias in children under fourteen years, Schlesinger found 37 lobar, the rest lobular in type. Holt states that after three years of age all primary pneumonias in children are lobar in character.

E Levy, Netter, and also Don have reported cases of congenital pneumonia. Fox and Lavenson have reported a case of pneumonia in the newborn due to the *Bacillus mucosus capsulatus*. According to Beddard pneumococcal pneumonia in adults is always lobar; in children it may be either lobar or lobular.

The duration of the disease is apt to be shorter than in adults, three- and five-day cases being often seen. The termination by crisis occurs in 68 per cent. of the cases, according to Morse. Pseudocrises are rare but irregularities and remissions not uncommon. The respirations may range from 50 to 80, the pulse from 150 to 170 in infancy. The last-named observer found otitis media in 18 per cent., empyema in 8 per cent., and the prognosis good if the temperature did not exceed 103° F. In infants, nursing becomes difficult, sometimes impossible. Retraction of the diaphragm is often noticeable. Crying as the result of pain is not frequent and when present is suppressed and hoarse. An expiratory grunt coupled with fever is often very suggestive. Absence of the knee-jerks, sometimes spoken of as *Westphal's sign*, has been considered of diagnostic value especially in differentiating pneumonia from meningitis.

It is often impossible to distinguish clinically between lobar and lobular pneumonia in childhood, a fact which is doubtless responsible for the diverse statements which are made. West[1] calls attention to the fact that acute pneumococcal inflammation in children often occurs in a disseminated form. He finds, too, that many cases of bronchopneumonia in children occur without an antecedent bronchitis, beginning and ending just like the acute pneumonia of the adult. However, both the physical signs during life, and in fatal cases the postmortem examination demonstrate, not massive consolidation, but disseminated patches. Subcutaneous emphysema as a complication sometimes occurs, generally, however, as the result of pertussis and bronchopneumonia.

The *first sign* noted is listlessness and indisposition to play, accompanied by a flushed face. Very suggestive is the disturbance of the respiration-pulse ratio. When this departs from the normal of 1 to 4 (20 to 80 per minute) and approximates 1 to 3 (40 to 120 per minute), expect further indications of pulmonary disease (O'Dwyer). Next to these, Northrup has found the following factors of respective importance: absent or diminished respiratory murmur over one lobe or portion of a lobe; rales of any kind, perhaps appearing only late, either in a localized shower, or diffusely scattered; bronchovesicular breathing —a bronchial whiff; slight dulness, becoming marked only late; and, lastly, cough.

[1] *British Medical Journal*, 1904, ii, p. 904.

It is well to bear in mind that pneumonia is very common in children, but frequently unsuspected and overlooked. Infants and small children often have no cough, and swallow what expectoration they have. Below the age of four, empyema is frequent. Koplik states that in certain epidemics meningeal symptoms predominate, especially if the apices are involved. The frequency of convulsions at the onset is probably overrated. The infant with pneumonia is apt to persistently refuse food, and to drink with reluctance at long intervals. Various forms of erythema may occur, but herpes, according to Wells, is infrequent. Serious complications are more common than in adults; among these, empyema and otitis media may be especially mentioned.

Termination.—Among 10,159 cases of pneumonia collected by the writer, the disease terminated by crisis in 5397, or 53.1 per cent. In 4718 cases the crisis occurred between the fifth and the ninth days in over 75 per cent. Cases are usually said to end by crisis when the temperature falls from a considerable elevation to normal or below it within thirty-six hours. The average time is generally shorter, from six to twenty four hours being required for the defervescence. Jürgensen has reported a case in which only four hours were consumed. It is not at all uncommon for the temperature to fall to several degrees below the normal and remain there for several hours or even days. A prolonged subnormal temperature usually indicates systemic exhaustion. Lebert tabulates the duration of the crisis in 110 cases as follows: twelve hours in 45 cases, twenty-four hours in 25 cases, and thirty-six hours in 40 cases.

Crisis is more apt to occur in children than in adults, in adults than in the aged, and in brief than in protracted cases. Lysis, on the other hand, is seen more frequently in the aged and in those enfeebled by acute or chronic disease. Among 8667 collected cases, 2161 (24.9 per cent.) terminated by lysis. Such an ending of the disease also occurs in atypical varieties, such as are due to other organisms than the pneumococcus, or those in which there is mixed infection. There seems to be a tendency at certain times in different epidemics for pneumonia to terminate preponderatingly by crisis or by lysis. Cases defervescing by lysis should always make us consider the existence of complications.

The crisis is often accompanied by extreme exhaustion and relaxation, a condition which is manifested by sweating, a rapid, weak, irregular pulse of very low tension, frequently dicrotism, epistaxis, profound sleep, polyuria, diarrhœa, and occasionally incontinence of urine. Crisis occurring as late as the nineteenth day of the disease has been reported.

Pseudocrisis consists in a rapid fall of the temperature which closely simulates the termination of the disease, but which is followed in the course of a few hours by a subsequent rise of the fever to, or even above, its original height. In favorable cases the pseudocrisis is followed in the course of a day or two by the true crisis. Among 1854 collected cases 172 had pseudocrisis (9.8 per cent.).

As regards the mechanism of crisis Dick states that proteolytic ferments appear in the blood during pneumonia about the time of crisis and believe these ferments may have a special action upon pneumococcus protein.

The crisis has received many explanations—antitoxin formation, bactericidal substance, and lately bacteriotropic bodies. Dochez[1] has shown that the serum of patients convalescent from pneumonia generally contains protective substances, especially at the time of the crisis, and if used on homologous strains of the pneumococcus. Similar conclusions were reached by Eggers.[2]

Duration.—The duration of lobar pneumonia ranges from one day to three weeks. Naturally the majority of the cases are not to be classed at either end of this limit; most of them last from five to ten days. In children three- and five-day pneumonias are by no means rare; and no less an authority than Aufrecht believes that even in adults "one-, two-, or three-day pneumonia" is commoner than generally supposed. The author saw a prolonged violent chill followed by a temperature of 105°, pulse 120, respirations 26, associated with pain in the side in an adult suffering from bronchitis. Within twelve hours the temperature was normal, to remain so, while a profusion of herpes appeared on the lips. Here apparently a pneumococcus invasion had been checked in an early stage. Musser saw a case of two-day pneumonia with all the characteristic symptoms and signs; the bronchial breathing lasted four days after the crisis. Aufrecht states that "many a status febrilis, many a febris ephemera, whose cause cannot easily be found may etiologically belong to this group of pneumonias."

In contradistinction to brief or abortive pneumonia we have *delayed resolution,* migratory and recurrent pneumonias. The first-named condition is met with chiefly in old and debilitated subjects. It must always be borne in mind that delayed resolution may be very closely simulated by tuberculous pneumonia, by chronic apical infiltration, by interlobar empyema or pleural effusion. Delayed resolution was reported in 105 among 2548 cases (4.1 per cent.). McCrae found the right lower lobe affected much more frequently than any other in delayed resolution. Under normal conditions resolution is accomplished through a process of autolysis, the metabolic changes being very closely allied to those which occur during the digestion of proteids.

Flexner has shown that the intensity of the autolytic power varies in the different stages of the disease, the highest activity being encountered during the stage of gray, and the lowest in the stage of red, hepatization, a condition which is perhaps due to the larger number of leukocytes present in the former. In unresolved pneumonia both autolytic power and leukocytes are low. Flexner attributes the failure of the exudate to be absorbed to the disproportion between leukocytes and other constituents. Opie has shown that failure of autolysis is, at least in a measure, due to the presence in the blood serum of an antilytic substance. In the processes of autolysis amino-acids are produced which can be demonstrated in the urine (Simon).

Andral was the first to describe *termination in fibroid induration* in unequivocal terms. Stokes described a case followed by marked retrac-

[1] *Journal of Experimental Medicine*, 1912, xvi, p. 665.
[2] *Journal of Infectious Diseases*, 1912, p. 48.

tion of the chest wall, empyema having been definitely excluded. Clinically delayed resolution is apt to be confused with old tuberculous lesions, secondary tuberculous infections, tuberculous pneumonias, and especially interlobar empyema. Fraenkel found that in every instance there were evidences of connective-tissue formation in the aveolar exudate. He states that in every case in which resolution is delayed beyond three weeks without definite cause — complications, such as abscess formation, etc.—we must assume that fibroid induration has begun. Macroscopically two varieties, the red and the gray, as originally described by Andral, are to be noted, having more or less the appearance of polished granite, the reddish hue being due either to the vascular richness of the tissue or to newly formed capillaries. Later the color fades to grayish yellow, as the result of fatty degeneration of the alveolar tissue. Months later the involved areas become pale gray, indurated, shrivelled, and of a tough consistence.

In delayed resolution there is continued fever, gradually subsiding in favorable cases. In drunkards and cachectic individuals a fatal termination is not infrequent. In this class the fever increases, becomes more irregular, and not infrequently leads one to suspect that the disease may have been a tuberculous pneumonia from the onset. Death may occur suddenly but usually ensues as the result of gradual heart failure, the fatal termination being frequently preceded by delirium, coma, etc. In some cases, as was pointed out by Wagner, the percussion dulness, bronchial breathing, and rales may gradually disappear, as the result of a compensatory emphysema of the surrounding tissue, and by the resumption at least in part of activity by the infiltrated area. According to Charcot these cases do not develop bronchiectasis; however this may be, it seems that a fibroid induration of the lung does predispose to other pathological changes, notably gangrene. These cases may be closely simulated by serofibrinous or purulent pleural exudates, interlobar empyema, and abscess of the lung. Exploratory puncture, careful microscopic examination of the sputum and the leukocyte count, will often help in the solution of the problem. The absence of fever is strong evidence against the presence of abscess or empyema.

S. West has drawn particular attention to the sequence of *chronic bronchitis* and of *emphysema* after pneumonia and to the need of proper after-care of pneumonia patients to prevent these sequelæ.

Relapse.—To avoid misunderstanding and to simplify the terminology in pneumonia it is well to limit the term "relapse" to those cases in which a fall in temperature accompanied by undoubted evidences of beginning resolution is followed by a fresh attack of pneumonia which invades the same location as the original one.

Relapse in pneumonia is rare. Osler states that he has seen but 2 cases. Among statistics, 36 instances occurred in 5966 pneumonias (0.6 per cent.). Chatard found 5 in 658 pneumonias. Fraenkel encountered 7 relapses in 1000 cases. More than one relapse may occur; Grisolle saw 3 attacks in the same individual within twenty-seven days. The duration of a relapse is usually short. Second attacks occurring after a long period of time must of course be considered as recurrent

infections. Sometimes there is a tendency for the disease to recur in the same portions of the lung.

Death.—Death in pneumonia usually comes on gradually with the signs of cardiac failure. The pulse progressively weakens, finally becoming irregular and intermittent. The respirations grow more superficial and ineffectual. The cough subsides and the sputum is no longer expectorated but blocks the bronchial tubes. The extremities become cold and the skin clammy. Cyanosis is replaced by an ashen-gray pallor; and, finally, pulse and respiration cease. Sometimes during the last few labored respiratory efforts the patient starts up convulsively and takes a last conscious glance at his surroundings, but, as a rule, death comes on insidiously. The stage of dying, as a rule, lasts several hours, but at times the end comes suddenly and unexpectedly, as the result of cardiac or pulmonary thrombosis. If death be due to severe toxemia, there may be few signs of circulatory failure until near the end.

Sudden death generally occurs during the stage of gray hepatization, and in such cases often neither the seat nor extent of involvement, nor the apparent gravity of the case, seem to bear any constant relation. It is usually precipitated by sudden exertion. Sudden death in children has been reported. Death may occur suddenly when convalescence is apparently well established. The day of disease on which death occurs may be the first of the attack, any day during the first three weeks, or even later. Out of 2613 collected cases 56.75 per cent. died between the fourth and eleventh days inclusive; 17.03 per cent. died after three weeks. The author has seen sudden death caused by pulmonary infarction which on softening ruptured into the pleura causing a pneumothorax, in a patient in whom there was no endocarditis. The infarcted area was surrounded by typical pneumonic hepatization.

Pneumonia may terminate in a general *pneumococcus septicemia,* or by metastatic suppurative foci in practically any part of the body. Such infection may be carried either by the lymphatics or the blood stream. Pneumococcic infection in various organs or tissues may of course occur without a preceding pneumonia. In such cases it may be impossible even at autopsy to determine the origin of the infection.

In cases of general or localized pneumococcus infection without the occurrence of a preceding pneumonia, we quite commonly find *four cardinal symptoms* present which are very suggestive of the condition, namely: chill, sudden pyrexia, leukocytosis, and herpes. One or more of these symptoms may occur in a variety of other morbid processes, but the simultaneous appearance of all of them in a given case should make us very strongly suspect the pneumococcus as the etiological factor. Definite information may be obtained from blood cultures, lumbar puncture, etc. Pneumococcus septicemia, secondary to local infection, has been reported by many writers.

Experimentally it is very rarely possible to produce a pneumonia by inoculation with the pneumococcus unless the animals are first partially immunized. This offers an explanation why in man after infection by the pneumococcus, in place of a rapidly fatal septicemia, the lungs

sustain the brunt of the assault, and in this situation there is set up a localized inflammation.

Physical Signs.—But little information of practical value can as a rule be obtained by *mensuration* of the chest. Certainly the data obtained by this method are not commensurate with the time required, or with the discomfort given to the patient. Diminished excursion of the diaphragm or of the chest is often observed on inspection. If the pain is severe, inspiratory expansion may be limited. Immobilization of the affected side does not occur to the same extent as in pleural effusion. Compensatory excursion on the healthy side may occur, as well as abnormally increased action of the accessory muscles of respiration.

Percussion and *auscultation* give most important data. During the early congestive stage a hollow tympanitic note is generally encountered. The congested alveolar epithelium and distended capillaries lessen the elastic tension and relax the pulmonary tissue. In a relaxed lung the percussion vibrations cannot be limited to a given area; the lung vibrates as a whole and therefore yields a tympanitic note. As consolidation begins dulness replaces the tympany, although as Thomas has pointed out, a tympanitic quality may remain, this being especially noted when the apices are involved, in which case as the result of imperfect consolidation in the early stages, tympany is more marked, and later, dulness is less intense.

In the early stage of a central pneumonia there may be hyperresonance of the entire chest, at times to such an extent as to make the sound side seem relatively dull, and hence a mistake may be made as to the side affected. In cases of central pneumonia the resonance may never become more than "impaired." Another explanation places the origin of the tympany in the vibration of the air within the bronchi which are surrounded by consolidation, as the result of which the percussion impact is transmitted with greater intensity to the bronchus, and the vibrations are in turn conducted back with more distinctness. Jürgensen mentions two cases in which percussion of the completely solidified lower lobes produced typical tympany, the pitch changing when the mouth was opened and closed. Sometimes when the lower lobes are involved tympany may result from the proximity of the stomach. Hyperresonance often occurs as the result of compensatory action on the part of the healthy lung tissue; in some cases it covers a neighboring lobe to that which is diseased; in others the entire opposite side of the chest is affected, this being largely dependent upon the extent of the consolidation. A cracked-pot sound may occasionally be elicited, when infiltration surrounds a large bronchus, especially in cases of complete apical consolidation, if the listener's ear be close to the patient's open mouth, and staccato percussion is employed. The area of dulness tends to be somewhat larger than the consolidated area. Associated with the dulness there is a distinct sense of resistance felt by the percussing fingers, which is sometimes more striking than the actual change in resonance.

In extensive consolidation, dulness may almost reach the degree of flatness, although the latter condition is always suggestive of pleural exudate, either plastic or liquid. When the upper lobes are first involved,

dulness quite frequently first appears in the posterior axillary line, and if at a high level, it may be overlooked. In all cases in which pneumonia is suspected and cannot be definitely made out, the upper axilla should be carefully percussed and auscultated. Wintrich states that "pulmonary tissue devoid of air and peripherally infiltrated gives a short weak note on percussion only if the space devoid of air has a diameter of about five centimeters and a depth of two centimeters, and then only upon superficial percussion." For this reason small areas of involvement may be difficult to determine.

Associated with the *crepitant rale* in the early stages, we generally have more or less suppression of the vesicular murmur, later vesiculobronchial, bronchovesicular, finally bronchial (tubular) breathing. When true bronchial breathing exists crepitant rales disappear. Suppression of the vesicular murmur is very common, and often the condition persists over the greater part of the consolidated area throughout the attack, especially in asthenic cases. This is the result of imcomplete, diffuse infiltration or obstruction of the small bronchi through excessive secretion. The fact that bronchial breathing may be absent is often very puzzling to the young practitioner who has acquired the idea that in all cases of pneumonia loud tubular breath sounds are to be heard. One not infrequently has to make a diagnosis of pneumonia on slight percussion dulness, suppressed vesicular murmur, a few subcrepitant rales, fever and increased respiratory rate. In typical sthenic cases, however, the breath sounds going through the stages mentioned, finally become loud, and typically tubular in character. Bronchial breathing may be heard during both inspiration and expiration; its intensity depends largely upon the completeness of the consolidation. It gives one the impression of sounds produced very close to the ear.

The statement made by Laennec that the crepitant rale is the most characteristic sign of pneumonia still holds good, although of course it is not pathognomonic. It is heard during inspiration, chiefly during the latter half, and consists of showers of fine, high-pitched, resonating sounds which have been aptly compared to the crepitation produced by the rubbing of a lock of hair held close to the ear, to the crackling of a static electric machine with the poles closely approximated, or the sound produced when salt is thrown upon a fire. Crepitant rales are produced by the inspired air breaking through small collections of tough secretion at the point at which a terminal bronchiole merges into an alveolus. They must not be confounded with subcrepitant rales which are heard in œdema of the lungs, hypostatic congestion, and catarrh of the finest bronchioles. They differ from the latter in that the sounds are finer, higher-pitched, more ringing, metallic, and dryer in character; they are also less influenced by coughing. The crepitant rale is produced in the lung only when the above described conditions of localization of secretion are accompanied by some consolidation, as in early pneumonia, tuberculosis, hemorrhagic infarct, or atelectasis. It may, however, be very closely simulated by the subcrepitant rale and by a fine pleural friction. The crepitant rale is one of the earliest signs of pneumonia; it may be only intermittently present for obvious reasons, and disappears

entirely when consolidation becomes complete, to return later on as "crepitus redux" when resolution begins, at which time it is often replaced by subcrepitant rales. It is heard only over the pulmonary tissue.

In cases with marked consolidation and bronchial breathing, uncomplicated by pleural effusion, loud high-pitched *bronchophony* occurs, which results from abnormally intense conduction through the solidified lung tissue. Bronchophony occurs only when consolidation is complete. It is more common in men than in women, owing to the fact that the size of the resonator—the thorax—stands in a more favorable relation to the vibrating vocal cords. At the end of a spoken syllable, a short, harsh, rough expiratory puff may be heard, which the last-named author explains as "very likely due to the more passive expiratory collapse of the thoracic wall."

Associated with bronchophony, due to the same causes and subject to the same exceptions, we find increased *vocal resonance and fremitus.* This generally allows us to exclude the presence of pleural effusion, but its absence permits of no positive deductions. It may be temporarily absent owing to excessive bronchial secretion; in such cases cough may cause its reappearance. In some cases it is persistently diminished or even absent. Gerhardt states that in cases with intense consolidation, such as those in which at autopsy the outlines of the ribs are furrowed upon the periphery of the lung, fremitus is absent. A thickened pleura may cause similar results. Much less weight can be attached to the condition of the vocal fremitus than to the findings of auscultation and percussion. When the lower lobes are involved the signs both on percussion and auscultation are earliest manifest posteriorly near the hilus of the lung.

Graves called attention to the fact that disseminated beating synchronous with the heart's action may be noted in the early stage of pneumonia; and likens the condition to a half-filled sack of fluid. Skoda described a pulsation of the hepatized area, not infrequently synchronous with the heart, a condition probably due to arterial pulsation in the engorged lung.

Connor and Dodge[1] carefully studied 392 cases of pneumonia in the early stages, with the intention of learning the *relative importance of the various physical signs.* Their findings are tabulated in the order of importance as follows:

1. Circumscribed area of feeble and indistinct breathing compared with the opposite side.
2. Circumscribed impairment without or with a tympanitic quality (sitting up).
3. Crepitant rales.
4. Slight increase in intensity and clearness of vocal resonance.

Occasionally we find abnormal physical signs on the sound side of the chest. Thus when consolidation exists at the root of one lung, we may have a transmission of bronchial breathing to the opposite side. Not infrequently we find some dulness and rales on the sound side,

[1] *American Journal of the Medical Sciences*, 1903, cxxvi, p. 389.

without there being any actual consolidation. This arises from the fact that one lung being in part consolidated, there is a tendency for more blood to pass through the sound lung; and if there is any weakness of the right heart it is apt to stagnate there; in addition, the vicarious breathing on the sound side produces more negative pressure, so that blood flows in more freely from the pulmonary artery.

The X-ray.—The employment of the *x*-ray does not enable us to distinguish definitely between lobar and lobular pneumonia or to make a diagnosis of consolidation before this is demonstrable by physical signs except in cases of a true central lesion. In this condition if the process remains localized the *x*-ray is the only positive diagnostic criterion. Radioscopic studies have shown that in many cases of pneumonia there is a considerable daily variation in the amount and location of the tissue involved. The onset of resolution can sometimes be determined before it is demonstrable by physical signs or temperature changes. Tuberculous infiltrations may appear almost as rapidly as true pneumonic lesions, but once present generally remain so. If, therefore, an infiltrated area changes its position or begins to clear up it is in all probability not tuberculous in origin.[1]

CLINICAL OBSERVATIONS

Complications.	Total cases.	Number with.	Per cent.
Albuminuria	4,792	2,184	45.58
Pleural effusion	24,511	1,535	6.26
Chronic nephritis	7,080	193	2.73
Empyema	13,550	303	2.2
Jaundice	22,544	373	1.65
Pulmonary tuberculosis	19,638	343	1.7
Acute pericarditis	40,773	499	1.2
Acute nephritis	30,042	367	1.22
Phlebitis	2,360	17	0.72
Abscess of lung	12,030	76	0.63
Cirrhosis of liver	3,644	19	0.52
Acute arthritis	28,645	150	0.50
Gangrene of lung	27,761	136	0.49
Acute tonsillitis	4,052	16	0.46
Acute endocarditis	32,349	144	0.44
Acute meningitis	49,028	206	0.42
Acute parotitis	2,655	10	0.37
Acute peritonitis	8,132	28	0.34
Pregnancy	13,611	120	0.8

AUTOPSY RECORDS

Complications.	Total cases.	Number with.	Per cent.
Pleural effusion	974	405	41.58
Nephritis (acute)	7020	1334	19.00
Nephritis (chronic)	2218	573	25.83
Acute pericarditis	2128	267	12.6
Otitis media	54	4	7.41
Acute endocarditis	2693	157	5.8
Gangrene of lung	1914	100	5.2
Empyema	973	50	5.1
Acute meningitis	4833	180	3.5
Abscess of lung	1294	28	2.1
Acute peritonitis	971	21	2.1
Acute arthritis	698	4	0.58
Pulmonary thrombosis	1830	5	0.27
Acute hepatitis	293	155	52.9

[1] "Die Pneumonie im Röntgenbilde," by R. v. Jaksch and H. Rotky, Hamburg, 1908; Fortschritte auf dem Gebiete der Röntgenstrahten, Ergänzungsband, 19.

Complications. — The true *complications* of pneumonia are really expressions of the pneumococcus infection in other organs and tissues than in the lungs. The foregoing tables, arranged in order of their frequency, show the results of collected cases.

Pleurisy.—Among the complications which may arise in the lung itself, we may begin with the commonest—*pleurisy.* Pleuritis occurs in *practically all the cases,* or at least in those cases in which the inflammatory process reaches the surface of the lung. It usually corresponds to the location of the pneumonia, although occasionally it may be met with on the opposite side. It is recognized by the well-known symptoms and signs—pain, restriction of motion, and a friction rub on auscultation. The latter symptom may be transient and often difficult to differentiate from intrapulmonary rales. These so-called dry pleurisies are often accompanied by a plastic exudate, which later on may give rise to adhesions, and thickening of the serous membrane.

Small liquid effusions are apt to be overlooked during the active stage of the disease and to become apparent only after resolution has begun.

Maragliano by using the exploring needle was able to demonstrate serofibrinous, or fibrinopurulent exudate in 38 out of 58 cases (65.5 per cent.). The adult pleura must contain 400 cc. of liquid before its presence can be demonstrated by physical signs.

Laryngitis and Bronchitis.—Laryngitis and bronchitis may precede or complicate pneumonia. *Bronchitis* is practically always present, and it is often difficult to say at what point a bronchitis should be considered a complication or merely a part of the disease, it being largely a question of degree and of distribution. Hyperplasia of the bronchial lymph nodes is constant. Recent bacteriological research shows that acute infections of the upper respiratory tract may be caused by the pneumococcus. It is probable that such infections under favorable conditions directly lead to an attack of pneumonia. A complicating bronchitis or laryngitis may therefore really be the initial infection. *Laryngitis* is much less frequent, and may be a serious complication, as in a case reported by Thornton in which an œdematous condition necessitated a tracheotomy at the onset of the disease, but in which recovery eventually occurred. In two cases seen by Landgraf, laryngoscopic examination, prompted by aphonia, disclosed marked congestion of both the true and the false cords, with deep ulceration which healed slowly. Two cases of *atelectasis* occurring in pneumonia are mentioned by von Jaksch. Suppurative *perichondritis* has been reported by Collier and Barwell. Primary acute pneumococcic *œdema of the larynx* followed by pneumonia and septicemia has been reported by Chauffard and Laroche.

Empyema.—Empyema occurred clinically among 13,550 collected cases in 2.2 per cent., and at autopsy was found in 5.1 per cent. of 973. As Preble points out, it is curious that the pneumococcus, which in the lungs only rarely produces suppuration, does so with great frequency when it attacks the serous membranes. Among his 45 cases of empyema, pyopericardium occurred once, pneumococcus endocarditis three times, arthritis once. In 288 cases of empyema in children at the Mt. Sinai

Hospital, New York, pneumonia was the etiological factor in 182. Ewart has called attention to the fact that in children 75 per cent. of all empyemas owe their origin to the pneumococcus, and 25 per cent. to the *Streptococcus pyogenes*, but that in adults this state of affairs is reversed. Empyema generally occurs during the stage of resolution. Pneumonia complicated by empyema rarely terminates by crisis.

In 500 cases of pleuritis collected from the records of the Pennsylvania Hospital, Philadelphia, by F. Fraley, there were 95 cases of empyema. Of these 48 gave a history of having had previously one attack of croupous pneumonia, 3 had had two attacks, and 2, three attacks; of these 95 empyemas, 35 immediately followed croupous pneumonia. Pneumothorax was noted 4 times in 95 empyemas and 4 times in 405 cases of non-purulent pleuritis. Abscess of the lung followed empyema 4 times. Twenty-one out of 95 died (22 per cent.). The following terminations were encountered: One ruptured through the diaphragm—peritonitis, 2 ruptured into the lung, with evacuation through the bronchus, and 1 ruptured externally. In 46 out of 95 empyemas the following organisms were found: in 1, tubercle bacilli; in 24, pneumoccoci; in 10, streptococci, and 11 were sterile.

The *symptoms* of metapneumonic empyema consist of fever, continuous with or coming on after that due to the pulmonary inflammation. Chills may occur, but generally do not, except at the onset of the fever, which often rises rapidly to a considerable degree. Sweats are of frequent occurrence, especially at night, but pain and dyspnœa are rarely noted. Leukocytosis is generally found and is very suggestive, especially if it reappears after a postcritical absence. The *physical signs* are those of pleural effusion and need not be dwelt upon, save to say that the exploring needle and the *x*-ray should be repeatedly used in doubtful cases, for when the exudate is encysted or between the lobes, a positive diagnosis may be impossible without their aid.

The exudate of a pneumococcus empyema is odorless, thick, greenish yellow, and rich in cellular elements. Microscopically the leukocytes are mostly of the polymorphonuclear variety, mononuclears and endothelial cells being relatively few in number. Generally the pneumococcus is found; sometimes there is a mixed infection with pyogenic cocci, such cases being more severe in character and accompanied by a higher mortality. Sometimes spontaneous absorption may occur but such an event should never be expected or awaited. Occasionally aspiration may bring about a cure, but generally resection of the ribs is necessary. If let alone, the pus may rupture into neighboring structures such as the lung, bronchus, or pericardium. External rupture through the intercostal spaces has occurred, but is of great rarity. Œdema of the overlying skin is very infrequent.

Netter states the metapneumonic empyema ruptures into the bronchus in about one-fourth of the cases. When spontaneous evacuation occurs, it generally does so during the third or fourth week, rarely before the third or after the sixth. Such an event may be suspected if there is a sudden expectoration of large amounts of purulent matter, and a lessening of the intensity of the physical signs, of the temperature, or of the

general constitutional symptoms. The operative mortality in this class of cases is low, ranging from 2 to 5 per cent.

Pneumothorax.—Among the very rare complications of pneumonia, pneumothorax should be mentioned. This is most frequently met with in cases of empyema, as the result of the latter rupturing into the bronchus or lung. Fismer found 2 such cases among 230 pneumonias. Empyema is not, however, a necessary factor. In an analysis of 51 cases of pneumothorax, Morse found 3 in cases of pneumonia complicated by abscess, and one by gangrene of the lung. In none of the abscess cases were there any symptoms at the time of onset. The physical signs were discovered on the seventh, fourteenth, and twenty-sixth days respectively after the onset of the pneumonia. In all of them the pneumothorax was open and purulent.

Abscess of the Lung.—Abscess of the lung occurred clinically in 76 among 12,030 cases (0.63 per cent.) and at autopsy was found in 28 of 1294 cases (2.1 per cent.), a frequency which can by no means be ignored. Among 658 cases of lobar pneumonia at the Johns Hopkins Hospital 5 had single and 4 multiple abscesses. At the Pennsylvania Hospital, Philadelphia, Fraley found 4 cases of pulmonary abscess among 500 cases of pleuritis. Two followed pneumonia; in the remainder no definite cause could be established, although pneumonia was suspected, as both were associated with empyema. Holt states that in 7 per cent. of the autopsies upon infants and young children dying of pneumonia, abscesses are found. They are usually small and, as a rule, multiple; they are rarely clinical conditions. In the past, abscess of the lung and empyema have been frequently confused and reasonably enough, for the symptoms of the two conditions may be similar, especially if the former is situated near the surface of the lung. Grisolle's study based upon 29 cases, shows that abscesses are generally found near to the surface, measure from 3 to 5 cm., have an irregular sinuous outline, their walls being bounded by shreds and tissue detritus. In rare cases a limiting membrane is found. Abscesses vary in size, may rupture into the pleura and have been known to empty themselves into the pericardium. Rupture into the esophagus has occurred.

Pulmonary abscess usually develops insidiously, producing no symptoms which are characteristic at first. The sputum is increased in amount and yellow in color, later becoming greenish. At times it may contain blood pigment, or assume a green or blue color by virtue of different chromogenic microörganisms. When the abscess is large the quantity of purulent expectoration may amount to several hundred cubic centimeters daily. In the later stages it is sometimes offensive. Both cough and expectoration often vary greatly with the position of the patient. Microscopically the sputum contains leukocytes, epithelial cells, bacteria, crystals of different kinds, and generally shreads of lung tissue. The latter are sometimes of sufficient size as to be recognized by an unaided eye. Elastic tissue and black and yellow pigment also occur. The particles of lung tissue constitute the characteristic feature. Fraenkel states the pneumococcus abscesses are larger than those in influenza pneumonia, which are apt to be diminutive and multiple.

The diagnosis, as Skoda long ago pointed out, cannot be made by auscultation and percussion alone. The cases pursue the course of a delayed resolution, with an irregular protracted fever, and at times hectic symptoms. "A probable diagnosis might be made if with the rapid increase of pneumonic symptoms a large quantity of pus, colored red by blood, should be brought up suddenly, followed by improvement in the phenomena of infiltration; the condition can be established with certainty only after the demonstration of lung tissue in the sputum." The recurrence of fever after crisis, if accompanied by profuse expectoration, should always call for a microscopic examination of the sputum. Radioscopic examinations are of value both for diagnosis and localization.

Gangrene of the Lung.—Pneumonia occasionally terminates in *gangrene of the lung.* This occurred clinically in 136 (0.49 per cent.) of 27,761 collected cases, and 1914 autopsy reports showed 100 (5.2 per cent.). As in abscess of the lung, alcoholism and general lack of vitality seem to be predisposing factors; among the latter conditions diabetes, nephritis, typhoid fever, and insanity deserve to be noted. The etiology of gangrene is uncertain; some cases follow abscess, others occur without it. When gangrene begins we find in the sputum, in addition to various pyogenic microörganisms, different saprophytic bacteria, through the agency of which necrosis of the pulmonary tissue rapidly occurs. The first symptom is an alteration in the character of the expectoration, which becomes brownish, more liquid, and finally prune-juice or chocolate colored. Microscopically the sputum shows, despite its manifestly bloody character, few, if any, red blood corpuscles, these cells having undergone solution as the result of the putrefactive process. From the same cause the particles of lung tissue are more minute than those found in abscess, they being barely visible to the naked eye. The elastic tissue also is no longer sharply outlined in contour. Hematoidin crystals may be encountered. As the morbid process advances the sputum becomes extremely offensive, often to such an extent that the whole room which the patient occupies is tainted with the putrid odor. The amount of expectoration may reach 1000 cc. per diem. Its color is grayish or greenish; when allowed to stand it separates into three layers, the uppermost containing mucus and necrotic tissue, which float on account of the air they contain; the second layer consists of liquid and the bottom of pus cells and necrotic debris. Bacteria are abundant, and in addition to the already mentioned substances, crystals of fatty acids, of leucin and tyrosin, of cholesterin and pigment may be found. Freshly expectorated sputum is generally alkaline in reaction, by virtue of free ammonia and alkaline salts; on standing it becomes acid from fermentative processes, during which butyric and other acids are produced.

Gangrene of the lung is accompanied by constitutional symptoms of great severity, by physical signs of delayed resolution, and if the patient lives long enough, by evidences of cavity formation. Occasionally infection of the pleural cavity produces an empyema, or rupture, a pyopneumothorax. Fetor of the breath may be absent, as in one of Wells' cases, and in 39 per cent. of those collected by Atkins. It must also be borne in mind that although fetor is very characteristic of gangrene

of the lungs, it may also occur, though to a less extreme degree, in abscess, bronchiectasis, ulceration of the bronchi, etc.

Gangrene occurs chiefly in those advanced in life. The gangrenous process may begin in an old tuberculous focus, or in a pulmonary abscess. Holt has reported a case in which an occlusion of the artery seemed to be the cause. Wagner has recorded a case in which a sphacelus of lung tissue, one by three inches in size, was found free in the pleural cavity; recovery followed an operation. Sometimes the gangrene is localized to the pleura. The author has recently seen pulmonary gangrene follow pneumonia in a man, aged forty-seven years, in whom the physical signs were practically negative until very shortly before death. At autopsy practically the whole lower half of the right lung was found destroyed.

Historical reports seem to show that gangrene of the lung is much more frequent in certain epidemics. Lepine states that it is more common in certain climates such as India, Malabar, and the coast of Coromandel. The two sexes seem to be equally affected. A complete tabulation of the reported cases of gangrene following pneumonia has been compiled by F. W. McRae.[1]

The main hope of recovery in abscess and gangrene of the lung lies in surgical intervention, for although patients undoubtedly do get well without operation, the number is much smaller in the latter than in the former event. Medical treatment except for general hygienic measures, fresh air, diet, etc., can only be symptomatic and is limited largely to the administration of drugs such as creosote, turpentine, oil of sandalwood, etc., which tend to decrease the fetor of the expectoration, general tonics, and stimulants. The following comparisons show what may be expected from the two methods of treatment. Even allowing for the fact that those surgically treated were picked cases, the figures are vastly in favor of surgery: In a series of 110 cases treated medically there were 79 deaths (71 per cent.), while Eisendrath gives the following statistics after operative intervention: of 25 acute simple abscess, 24 recovered (96 per cent.), 1 improved (4 per cent.); of 28 acute gangrene, 20 recovered (71.4 per cent.), 2 improved (7.2 per cent.), 6 died (21.4 per cent.); of 14 chronic simple abscess with bronchiectasis, 6 recovered (42.8 per cent.), 3 improved (21.4 per cent.), 5 died (35.8 per cent.); and of 26 chronic putrid abscess with bronchiectasis, 13 recovered (50 per cent.), 4 improved (15.3 per cent.), and 9 died (34.7 per cent.). Surgery may be expected to yield good results, when the lesion is limited to one lung, when its area is circumscribed and not diffuse, when it is single, not multiple, and when there are pleural adhesions. "It would be very poor surgery to attempt any interference in a gangrenous lung before nature had raised a barrier and limited the disease—that is before a line of demarcation or separation has formed" (Le Conte).

When death occurs as the result of pulmonary gangrene, it may be due either to suffocation, or collapse, both of which are much aided by coincident toxemia. If recovery ensues, we may find cavities of varying

[1] *Journal of the American Medical Association*, vol. xxxix, p. 739.

size, dependent upon the amount of tissue destruction, or extensive fibroid induration with cicatricial contraction. In such cases the patient's existence is often rendered almost intolerable by the continued expectoration of offensive sputum.

Subphrenic Abscess.—This is very rarely a sequel of pneumonia.[1] The diagnosis of "empyema" is usually made. The infection probably occurs through the diaphragm and in many cases pneumococci have been demonstrated in the pus.

Mediastinitis.—Mediastinitis is a very rare complication of pneumonia. It was found in 8 among 363 collected autopsies. Weichselbaum pointed out that in many patients dead of pneumonia, there were evidences of acute inflammation in the areolar tissue of the mediastinum, neck, and clavicular fossæ, as well as about the œsophagus, cervical vertebræ, and trachea. This was corroborated by Foa and Bordoni-Uffreduzzi. Finally, Thue succeeded in isolating the pneumococcus and tracing it from the lymphatics of the pulmonary pleura, to the mediastinum, and pericardium (Fraenkel). The last-named author has seen in all 3 cases, 2 of them having other complications; empyema and pericarditis twice; purulent peritonitis, endocarditis, and meningitis were also encountered.

In these cases there is often a general pneumococcus septicemia. Pöhlmann found one case in 129 pneumonias; in this there was also meningitis, pericarditis, and peritonitis. The diagnosis of mediastinal pleurisy is difficult, for though its existence may be suspected it is not until a careful search for physical signs has been made that a zone of limited dulness with absence of pulmonary bruit gives the diagnosis. In 2 cases this zone was close to the vertebral column at the level of the interlobar space. Operation was performed in both cases; the mediastinal pleura was incised and drained.

Occasionally the *bronchial glands* in pneumonia are so greatly enlarged as to cause pressure symptoms, although this is extremely rare. Tardieu has reported a case in which a loud systolic murmur was heard over the great vessels, which seemed to be due to this cause. In 127 autopsies made by Longcope at the Pennsylvania Hospital, Philadelphia, very marked swelling of the bronchial lymph nodes occurred three times.

Gastro-intestinal Complications.—These are most marked in asthenic cases, and also occur quite frequently as prodromes, especially in children. Collected statistics are as follows:

Complications.	Cases.		Present.	Per cent.
Vomiting	5047		1356	26.8
Nausea	991		134	13.5
Constipation	1459		151	10.3
Diarrhœa	5336		190	3.5
Abdominal pain	1129		13	1.1
Enteritis	2789		30	1.08
Intestinal obstruction	673		2	0.29
Gastric ulcer	245	autopsies in pneumonia	2	0.8

[1] The whole literature of this subject has been reviewed by Perutz, *Centralb. f. d. Grenzgeb. d. Med. u. Chir.*, 1905, vol. viii, No. 10.

Vomiting may result from gastritis, severe coughing, from toxic cerebral irritation or from a complicating meningitis. Acute dilatation of the stomach is a complication "fraught with great danger to the patient, usually easily relieved, and generally unrecognized" (M. H. Fussell). Organic disease of the stomach or intestines sometimes occurs. A few cases of pneumococcus gastritis are on record, the affection being either primary or secondary to pneumonia or ulcerative angina. A membranous *colitis* occurred in 1 of 173 autopsies reported by Kerr, and 5 times in Osler's series. The digestion is not as a rule seriously impaired except as the result of injudicious medication. *Diarrhea* may result from intestinal ulceration or from toxemia. Remedies calculated to check this symptom should therefore be administered only after due deliberation. *Hemorrhage* from the bowels may occur. Wells states that during an attack of pneumonia, patients harboring *intestinal parasites* often pass them in large numbers. Dieulafoy has described under the name of ulcerative and hemorrhagic pneumococcic gastritis a condition which may be productive of even fatal hemorrhage. It is accompanied by nausea, vomiting, and pain, and may terminate in peritonitis.

Meteorism is often present, being favored by restriction of movements of the diaphragm. If considerable in amount it may be due to peritonitis, septic enteritis, or toxic paresis. When marked it is one of the most unfavorable prognostic signs. Pneumococci can be found in the peritoneum in practically all cases of pneumonia. Measures aimed at reducing tympanites will materially influence the course and lower the mortality of the disease. Rutz contends that there are living and active pneumococci in the feces.

Peritonitis is one of the most serious complications. That this is rare is shown by the statistics of collected cases. It was found clinically in 28 among 8132 cases (0.34 per cent.) and in 21 among 971 autopsies (2.16 per cent.). Pneumococcic peritonitis may be either primary or secondary, circumscribed or diffuse. The only treatment for the circumscribed variety is early incision with ample drainage. This primary isolated form is the most common, especially in children. The sudden high temperature, palpation of an encysted effusion, and diarrhœa are the main features. The primary diffuse form presents a syndrome exactly like that of peritonitis secondary to appendicitis. Some recoveries are reported after operation in the secondary encysted form, but no recoveries are recorded from the secondary diffuse variety. Bennecke states that pneumonia in the right upper lobe is most liable to be accompanied by these peritoneal and abdominal symptoms. Cases presenting signs of appendicitis or peritonitis should be investigated most carefully for evidences of pneumonia. A number of unfortunate abdominal operations have been performed which might have been avoided by more careful examinations of the lungs. At the same time it is to be recalled that appendicitis may occur simultaneously with pneumonia or during convalescence.

As a general rule pneumococcic peritonitis is a primary infection or else part of a general septicemia. The symptoms do not differ from peritonitis due to other causes. From a practical standpoint its chief interest lies in the fact that it may be very closely simulated by the

reflex abdominal pain which occurs with considerable frequency in pneumonia.

Longcope has called attention to the fact that at least as a terminal complication, peritonitis in pneumonia is not so rare as the literature would lead us to suppose. In 23 consecutive pneumonia autopsies at the Pennsylvania Hospital, Philadelphia, well-marked peritonitis was noted 5 times. The pneumococcus was recovered in cultures in 3 cases, the streptococcus in 2. Coplin has shown that the diaphragm itself may be the seat of degenerative changes, but this may also occur in septicemias due to other organisms than the pneumococcus.

Cardiovascular System.—The *cardiac complications* are of extreme importance, not only concerning the immediate outcome but equally regarding the subsequent life and health of the patient. The infectious fevers are capable of exerting permanent and often marked damage upon the heart and arterial system, which, although it may not be apparent or be overlooked at the beginning, nevertheless institutes a series of changes evident at first through diminished capacity and later through manifest degenerations of the cardiovascular system. The effects of pneumonia upon the heart itself may be brought about through the toxemia or by the microörganisms themselves. In the former instance the damage is more apt to be of a transient nature, which if the disease itself be overcome, the course of time will remedy. The latter is more apt to leave behind a permanent organic lesion, the usual tendency of which is to become progressive.

Endocarditis.—As Bouillaud first pointed out, pneumonia is one of the causes of endocarditis. Since then acute endocarditis has been ascribed to pneumonic infection with the following frequency: Abraham, 1 out of 9; Banti, 8 out of 22; Desse, 14 out of 34; Harbitz, 9 out of 43; Trauz, 1 out of 6; Kanthack and Tickell, 14 out of 84; Lenhartz, 5 out of 38; Osler, 54 out of 209 (ulcerative); Jackson, 1 out of 5; Walter, 1 out of 21; and Weichselbaum, 6 out of 33. Pneumococci were first demonstrated in the valvular lesions of acute endocarditis by Meyer in 1887.

Acute endocarditis occurred in 144 of 32,349 collected cases (0.44 per cent.), and in 157 of 2639 autopsies (5.8 per cent.). The discrepancy between these figures shows that endocarditis is frequently overlooked. Pneumococcus endocarditis differs in several respects from other varieties of this condition. It is twice as common in women as in men and about three-fourths of the cases are ulcerative in character. Among 16 cases found by Osler in 100 autopsies, 5 were simple and 11 ulcerative; chronic endocarditis occurred in 21 out of 80 cases. The left heart is more often attacked than the right, but the right is more frequently diseased than is the case in other varieties of endocarditis. Netter found lesions in the right heart in one-seventh of his cases. "To put it another way: In 17.8 per cent. of the cases of pneumococcus endocarditis the right heart is affected, while only 6.7 per cent. of the cases of endocarditis in general are right sided" (Preble[1]). The aortic and pulmonary valves are oftener

[1] Preble, *American Journal of the Medical Sciences*, November, 1904, has collected 132 cases of pneumococcus endocarditis from the literature. From this excellent monograph many of the data have been taken.

diseased than the mitral and tricuspid. Wells found *cardiac thromboses* more frequently than in any other disease, 169 instances of antemortem clot in 777 autopsies (21.7 per cent.). *Infarction* takes place in about one-half of the cases; not rarely as is generally stated. About 60 per cent. of the cases are associated with meningitis, but when the latter is the primary complication, it is accompanied by endocarditis in about 30 per cent. Acute endocarditis is much more common over thirty years of age than in earlier life.

Patients with chronic endocarditis are more likely to develop an acute infection than those in which the endocardium is healthy.

Acute endocarditis is very readily and frequently overlooked, owing to the fact that in the majority of cases physical signs are absent, and when such exist they are generally overshadowed by those of the pulmonary disease itself. Systolic murmurs are very common in pneumonia, and those which are due to acute inflammatory lesions are in no way characteristic. As in other diseases diastolic murmurs are very suggestive, particularly since in pneumonia the valves at the base are so often affected. The most suggestive and often the only positive features are symptoms referable to infarction of different organs. If the spleen is affected we may find enlargement, pain, and tenderness; if the kidneys, pain and hematuria; if the lungs, pain, bloody sputum, and signs of consolidation; if the skin, petechiæ and ecchymoses. Boston has reported a case of acute endocarditis in pneumonia in which there was a small pneumococcic abscess in the wall of the right ventricle. Blood cultures may be of assistance in arriving at a correct diagnosis; Preble collected 9 cases in which this procedure had been positive, in some of which more than one attempt was necessary. Acute endocarditis complicated by abscess of the thyroid gland has been reported by Schlender.

The symptoms of pneumococcus endocarditis are similar to those of other varieties. Fever is generally present, may be continuous with that of the primary process, intermittent, or accompanied by afebrile periods of varying duration. Chills and hectic symptoms are by no means rare, but prolonged apyrexia is unusual.

The prognosis is extremely grave. In Preble's 132 cases there were but four recoveries and in one of these the diagnosis was in doubt. It is likely that unrecognized cases recover more frequently and indirect evidence of this is found in the fact that many patients with chronic endocarditis, in the absence of other previous infectious fevers, give a history of an antecedent attack of pneumonia.

As to the effect of *chronic endocarditis* upon pneumonia, Hay states that in well-compensated cases, the course of the disease is unaffected, except that delayed resolution is apt to occur. The writer's investigations lead to different conclusions. Of 114 cases of pneumonia complicated by chronic endocarditis 37 or 32.46 per cent. died, a figure certainly above the average mortality, although it must be borne in mind that a number of these cases were advanced in life and probably the subjects of renal disease.

Cardiac Arrhythmia.—As in other infections arrhythmia directly attributable to the toxins occasionally occurs either during or more

commonly after the febrile period. *Sinus arrhythmia* is seen especially in children. It is due to overaction of the vagus, and is of no pathological significance. *Extrasystoles* sometimes appear if cardiac excitability is increased or if vascular or pulmonary resistance is increased in disproportion to ventricular strength. The appearance of extrasystoles during the febrile period while unpropitious is not necessarily of ill omen, especially if the pulse-rate be moderate. The more rapid the pulse the more serious the portent of an extrasystole. *Heart block*, generally partial in type, postcritical in occurrence, and temporary in duration has been reported.[1]

Pericarditis.—Acute pericarditis, either serous, plastic, or purulent, occurred 268 times among 2128 autopsies (12.6 per cent.), and 499 times among 40,773 collected cases of pneumonia (1.2 per cent.). It is therefore by far the *commonest cardiac complication* and stands high up among complications in general. The wide variation in the frequency with which the condition is reported by different observers shows that even allowing for errors the condition is more frequent at certain times.[2] That pericarditis is frequently found unexpectedly at autopsy is well known. Friction sounds over the precordium are often transient and of short duration. Furthermore they are often obscured by rales, the breath sounds, and pleural friction.

Infection may occur through the blood or the lymph stream, but quite often results from direct extension from infected areas of the lungs and pleuræ. In a large proportion of Jürgensen's cases the lingual process of the left upper lobe was diseased. Pericarditis may appear during any stage of the disease but most often during the fastigium. The onset is unaccompanied by any characteristic symptoms or signs. The heart should be examined daily with care but even under these circumstances, detection may be impossible. The symptoms and physical signs are similar to those of pericarditis due to other causes. The seriousness of the *prognosis* is materially enhanced by this complication, which interferes both mechanically and by being associated with myocarditis. Among 207 cases, 125 died (60 per cent.). In 55 fatal cases of pneumonia Satterthwaite found that in 10 instances death was directly attributable to pericardial involvement.

Treatment should consist of the local application of cold to the precordium, and such other measures as the individual case may require. As soon as the presence of an effusion is even reasonably established, an exploratory puncture should be made, and if the exudate prove purulent in character the patient should be referred to the surgeon for resection and drainage, as this offers the only hope of recovery.

Vascular Lesions.—A fairly large number of cases of peripheral venous thrombosis are recorded in the literature. The condition is usually a sequel, though it may come on at any time. Of 41 cases, 9 died, 25 recovered, in 7 there were no data. In 5, death was due to pulmonary

[1] Dykes, *Lancet*, October 12, 1912.

[2] Netter found pericarditis in pneumonia during the years 1837, 1876, 1882, 1886, and 1890 much more frequently than in the intermediate years.

embolism. The condition is rare, despite the fact that in pneumonia the blood is rich in the elements which favor clotting. The lower extremities are nearly always the seat of involvement and the left side more often than the right, owing to the anatomical conditions. Steiner reports 51 cases of venous thrombosis from the literature and adds 3 more, encountered among 658 cases of lobar pneumonia at the Johns Hopkins Hospital. Pulmonary thrombosis is one of the causes of sudden death in pneumonia. The author found 1 case of pulmonary thrombosis in 127 autopsies. Other vascular lesions were: infarct of the lung 2, of the kidney 3, of the spleen 7. Among our collected cases pulmonary thrombosis occurred 5 times in 1830 pneumonias (0.27 per cent.), and peripheral thrombosis 17 in 2360 (0.72 per cent.).

Kredel's case of popliteal thrombosis necessitated amputation. Seidelmann saw symmetrical gangrene in the fingers and thumbs of both hands in a female, aged twenty-nine years, who developed double pneumonia twenty-nine days after giving birth to twins. Gangrene of the fingers of the right hand consequent upon pneumonia has been reported by McGregor. Hjelt has reported embolism of the abdominal aorta.

Embolism of the right lenticulo-optic artery was encountered by Aldrich. As a result of embolism one sometimes meets with spontaneous gangrene of the extremities. Cases recorded show that the legs, fingers, and toes have been lost; in some amputation was performed, in others spontaneous sloughing took place.

Renal System.—*Albuminuria.*—Albuminuria was found in 2184 of 4792 collected cases (45.58 per cent.). The vast majority of these are transient in character, and accompanied by a few hyaline casts, epithelial cells, and leukocytes; occasionally red cells are found, these representing a higher grade of renal irritation. It is not possible to make a sharp distinction between the so-called "febrile albuminuria" and mild grades of *nephritis,* the matter is simply one of degree, both processes being caused by the same factors, namely, the presence of microörganisms[1] or their toxins in the kidneys. When the organisms are numerous or the toxins virulent severe grades of nephritis may be produced. The question must therefore be decided largely by the duration. If the albuminuria is simply due to the fever, it will disappear with, or soon after, the crisis.

Nephritis.—Cloudy swelling of the kidneys is usually evident, occasionally, also, fatty degeneration. Acute nephritis, usually of the glomerular type, with proliferation of the capsular epithelium, may occur. In 30,042 collected cases, acute nephritis occurred in 367 (1.2 per cent.), and in 1334 autopsy reports it was noted in 255 (19 per cent.). Of 116 cases of acute nephritis in pneumonia, 76 died (65.52 per cent.). Nephritis may come on at any stage of the disease. Œdema is an uncommon symptom; hematuria is frequently encountered. The usual termination is in death or recovery, chronic nephritis being an unusual outcome. Among 127 pneumonia autopsies collected by the author from the records of the Pennsylvania Hospital, Philadelphia, the following pathological conditions were found: cloudy swelling in 45, acute nephritis

[1] Fraenkel and Reiche found the pneumococcus in the kidneys in 22 out of 26 cases

in 18, and chronic nephritis in 53. Hemoglobinuria has been reported by Nash and by Dowenspeck.

The Skin.—The skin may show various processes, but the majority are simply the result of coincidence. Thus erysipelas is occasionally encountered. Two cases of pemphigus have been reported by Beyer, who could find only two similar cases in the literature. In one of Beyer's cases pneumococci were recovered from the cutaneous lesions. Other occasional conditions reported are loss of hair, furunculosis, purpura, erythema multiforme, petechiæ, ecthyma, and herpes zoster, the last twice in 1065 cases. Collected cases give the following data:

Condition.	Cases.	Occurrence.
Erysipelas	8043	32
Loss of hair	1065	1
Furuncles	230	5
Purpura	949	1
Erythema multiforme	500	1
Petechiæ	486	1
Ecthyma	133	1
Herpes zoster	1065	2

Underwood has reported a case of purpura hemorrhagica as a sequel of pneumonia, in which there was also delayed resolution, arthritis of the left ankle, erythema, persistent epistaxis, and melena. An instance of pneumococcic metastatic dermatitis has been recorded by Wolkowioz. Desquamation sometimes occurs during convalescence on the face, principally on the nose and cheeks.

Jaundice.—The marked diversity of opinion as to the frequency of jaundice in pneumonia is to be explained by the fact that slight degrees easily overlooked and that its occurrence varies greatly in different epidemics. At the Johns Hopkins Hospital jaundice occurred in 76 out of 658 cases of lobar pneumonia (11.5 per cent.) Regarding its pathogenesis, numerous theories have been advanced.

Banti from a study of 15 cases concluded that hemolysis was brought about by the pneumococcus. His cases at autopsy showed patent bile ducts, inspissated bile and bile-stained feces. Microörganisms from these patients when injected into animals produced hemoglobinuria, those from others in which no jaundice existed failed to do so. McPhedran[1] in 14 cases of lobar pneumonia with and without jaundice, estimated the fragility of the red corpuscles and found an increased resistance in the jaundice cases. Increased fragility occurred only once and this without jaundice. Bilirubin was present in the urine in 3 of the 8 cases with jaundice. The blood counts pointed to a sudden and marked destruction of erythrocytes presumably due to hepatization. Inflammation of the parenchyma of the liver due to the pneumococcus has been described by Lemierre, who believes that the liver complication develops preferably in persons with preëxisting liver lesions. A number of writers have reported cholecystitis, duodenitis, and catarrh of the smaller bile ducts. When the jaundice is marked, nearly all observers have encountered a high mortality: Mosler 73 per cent., Fismer 20 per cent., Musser

[1] McPhedran, *Johns Hopkins Hospital Bulletin*, 1911, vol. xxii, p. 408.

25 per cent., and Norris 61 per cent. As Preble suggests, this high mortality is probably not alone dependent upon the actual intensity of the icterus, but also upon the etiology. These patients usually manifest all the symptoms of severe cholemia. Albuminuria is often caused or if already present is intensified by cholemia, and the sputum may be of a greenish hue. The term "bilious pneumonia" is obsolete.

Jaundice probably arises from a variety of causes: retention of bile, infection of the gall ducts, gall-bladder, or liver, hypostatic congestion, and hemolysis, the latter being of considerable importance. When cholecystitis is present, its symptoms are apt to be overshadowed by the primary disease. The character of such infection varies; in Gilbert and Grenet's cases it was the colon bacillus; in Clairmont's case, Friedländer's bacillus. Changes in the hepatic parenchyma, cloudy swelling, etc., may cause a perversion of function.

Enlargement of the Liver.—This is quite often encountered, the edge being palpable a short distance below the costal margin. This may result from actual enlargement, due to cloudy swelling, or may be only apparent, being merely a displacement downward, produced by massive consolidation of the right lung, pleural exudate, or subdiaphragmatic abscess. Gilbert and Grenet studied the size of the liver in 48 cases and found it palpable below the costal margin in one-fourth of the adult cases and in all instances among children, but not so in those of advanced age.

The collected statistics of *hepatic complications* are as follows: Of 22,544 cases, 373 or 1.65 per cent. had jaundice and of 344 so affected, 15.7 per cent. died; of 173 patients, 20.23 per cent. had a palpable liver, in 7 of whom the liver was tender; of 201 patients, 1 had perihepatitis and 1 had liver abscess; of 3644 patients, 19 (0.52 per cent.) had cirrhosis of the liver. Of 144 autopsies 5.55 per cent. showed nutmeg liver; of 517 autopsies, 5.03 per cent. showed cirrhosis; of 216 autopsies, 53.24 per cent. showed fatty liver; of 293 autopsies, 52.9 per cent. had acute parenchymatous hepatitis; of 400 autopsies, 2.25 per cent. had jaundice; of 127 autopsies, 1.5 per cent. had cholecystitis.

Nervous System.—Complications in the nervous system may be very varied. It is often difficult to determine just what relation the pneumococcus bears to the nervous system. For instance, Seitz has succeeded in cultivating this organism from the central nervous system of a patient dying of Landry's paralysis, who had no other evidences of such infection.

Meningismus is quite common in pneumonia, especially in childhood. This condition may arise from a variety of causes—reflex, toxic, febrile, otitis media—other than pneumococcic infection of the meninges. Primary pneumococcus meningitis may of course occur, but in the present article we are chiefly interested in the secondary variety.

Meningitis.—Councilman believes that the frequency of pneumococcus meningitis is greatly overestimated especially as secondary to pneumonia. The pathology is in general similar to that of epidemic meningitis, with the exception that purulent infiltration of the cord and brain and extension along the nerves is less marked, while endovascular lesions are more prominent. Among 49,028 collected clinical cases meningitis

occurred in 206 (0.24 per cent.), and at autopsy in 180 out of 4833 (3.5 per cent.). Aside from children, meningitis occurs chiefly in those debilitated from different causes. Fox collected 29 cases; 9 were in drunkards, 7 had red and 19 gray hepatization, 8 had empyema, and 1 suppurative parotitis; most of them occurred between the third and the seventeenth day.

The duration of symptoms was one day in 22 cases, two days in 19 cases, three days in 7 cases, four days in 6 cases, five days in 3 cases, six days in 1 case, seven days in 3 cases, eight days in 2 cases, nine days in 1 case, and eleven days in 1 case (Netter). The day of onset was on the third day in 1 case, fourth day in 1 case, sixth day in 4 cases, seventh day in 1 case, eighth day in 2 cases, ninth day in 3 cases, tenth day in 6 cases, twelfth day in 2 cases, and seventeenth day in 2 cases (Nauwerk).

The majority of the cases occur during the acme of the disease. Infection may take place through the blood, lymphatics, the areolar tissue beginning in the mediastinum and extending upward to the nose, accessory sinuses, or ethmoidal fenestrations. The distribution of the inflammatory process and exudate accounts for the great diversity of symptoms. Fraenkel has called particular attention to the fact that in pneumococcic meningitis the onset, and even the entire course, may be insidious. This was particularly the case in adults and occurred in 4 of his 5 cases; in one of them even rigidity of the neck was entirely absent. The earlier in the course of the disease the meningitis appears, the more striking are the symptoms. Cases of pneumococcic meningitis without symptoms have been demonstrated at autopsy by Liebermeister and by Oseki. In some of the cases the lesions were revealed only by microscopic examination.

In 489 cases of pneumonia the author found retraction of the head without meningitis in 3, headache in 10, stupor in 23, delirium in 77, subsultus tendinum in 16, convulsions in 5, hiccough in 1 (fatal), delusions and hallucinations in 1.

The symptoms when present are those of meningitis due to other infections, headache, vomiting, cervical rigidity and retraction, and delirium. If no more than these are present it may be impossible to decide whether we are dealing with a meningitis or not. The diagnosis must generally be based upon the appearance of more definite symptoms, such as neuroretinitis, paralyses of the cranial nerves, etc., slowness of the pulse, monoplegia, or hemiplegia. Generally the question may be definitely settled by lumbar puncture. In some cases the cardinal symptoms from the very time of onset are those of meningitis, definite signs of pneumonia making their appearance several days later. Occasionally the meningitis appears a long time after the pneumonia, as in a case reported by Aufrecht, in which it appeared two months after recovery from a pneumonia complicated by empyema, in which there had been no cerebral symptoms during the primary attack. The presence of meningitis adds very much to the seriousness of the disease. Undoubtedly some recover, but there is the suspicion that we may have been dealing with symptoms only and not with organic disease. Of 33 cases collected by the writer, 31, or 93.93 per cent., were fatal.

Coma and Stupor.—Coma and stupor may occur in pneumonia. They are unfavorable symptoms which occur most frequently in toxic cases and in children; they may be associated with headache, vomiting, and rigidity of the neck without there being a meningitis present.

Dilatation of the pupil on the affected side due to irritation of the superior cervical sympathetic, especially in apical lesions, is occasionally seen. The author examined 64 patients with special reference to the pupillary condition but found inequality only twice, although the upper lobe of the lung was involved in 33. In one case there was mydriasis, in the other myosis, of the affected side. Pupillary inequality is by no means infrequent in healthy people, especially when myopia and hypermetropia coexist, and it is common for the pupil nearer the source of illumination to be smaller than the other, so that we must eliminate a number of causes before ascribing pupillary abnormalities to pneumonia. Schultze has reported temporary absence of the light reflex.

Neuritis.—Neuritis as a complication or sequel has been reported by a number of observers. The diversity of the nerves involved suggests that the etiological factor is a toxic one. Neuritis of the nerves of the extremities, the nerves supplying the ocular muscles and the palate, and even multiple neuritis have been encountered.

Pirrone has demonstrated by experimental researches that the pneumococcus can produce an ascending neuritis, but that the nerves are not an easy route for the propagation of the inflammatory process toward the centres. The lesions grow less and less pronounced as they recede from the periphery.

Hemiplegia.—Hemiplegia in pneumonia may be embolic or toxic. Becker found 1 example of the former among 505 pneumonias in German recruits. Bernheim believes the emboli usually arise from thrombi in the pulmonary veins or small clots in the heart. Acute encephalitis has been reported by Mollard and Dufourt and by Weichselbaum. Transient hemiplegia and aphasia during convalescence have been reported by Antoniu. It is of course possible that these evanescent lesions are basically uremic. In a case of hemiplegia with aphasia reported by Vogelius the condition was brought about by necrosis of cerebral tissue. In 5 cases of tardy paralysis following pneumonia, meningomyelitis was found in 2, while the others presented no such lesion. *General paralysis* has been reported as a sequel by Gubler and by Macario. Tetanoid and choreiform manifestations occurring in man and wife, both the subjects of pneumonia, have been described by Kelynack, and *tetany* two weeks after pneumonia in a rachitic girl by Page.

Ocular Complications.—Ocular complications are occasionally seen. Two cases of conjunctivitis occurred in 141 cases. Becker in 505 pneumonias found 1 case of conjunctivitis and keratitis. Pneumococcus conjunctivitis is well known to ophthalmologists. Crispolti reports pneumococci in the conjunctival secretion in 40 out of 45 cases of pneumonia, while Randolph believes the conjunctival flora in persons suffering from pneumonia differs in no way from that of persons in perfect health. Mandl has reported a case of keratitis with perforation of the

cornea on the fourteenth day; the cultures showed pneumococci. Transient mydriasis, photophobia, and amblyopia have been described by Thomas, and distension of the retinal veins by Sichel and Seidel. A case of complete transient blindness following pneumonia has been reported.

Acute Otitis Media.—This occurs chiefly in childhood and may appear at any stage of the disease. The two conditions may be simple coincidences, infection of the ear may come through the Eustachian tube or the blood, the pneumonia may be secondary to disease of the ear, or the otitis may cause general sepsis and a septic pneumonia follows. According to Lermoyer and Helme hematogenous infection gives rise to more virulent inflammations, which is corroborated by the fact that in cases of general pneumococcus infection, extensive suppuration is apt to occur. Wells states that "One or both ears may be affected; rupture of the tympanic membrane is the rule; severe mastoiditis may occur; extension to the cerebral membranes or sinuses is rare. In these cases the mental dulness increases; pseudomeningeal symptoms may appear; rigidity of the neck is often, if not usually, present; tenderness is manifested when pressure is made on the lobe of the ear; recovery without impairment of hearing is the rule." Right-sided pneumonia is said to be more frequently complicated by otitis media. Among collected cases: Of 4885 patients, 62 (1.3 per cent.) had suppuration of the middle ear; of 1065 patients, 1 had suppuration of the external ear; of 949 patients, 2 (0.2 per cent.) had mastoiditis; of 500 patients, 2 (0.4 per cent.) had pain in the ear at onset; and of 1305 patients, in 8 (0.6 per cent.) more or less deafness followed. Metastatic pneumonia following otitis media has been reported by Hrach. Otitis media would be found more commonly if the middle ear were routinely examined at autopsy. Whenever symptoms suggestive of meningitis occur in pneumonia, an examination of the ears should be made; such symptoms have been known to disappear rapidly after puncture and drainage of the tympanic cavity.

Acute Parotitis.—Acute parotitis is a rare complication. In the literature references were found to 20 cases of parotitis complicating pneumonia. Among 2655 collected cases it occurred in 10 (0.37 per cent.). The symptoms consist of tenderness, swelling, painful secretion of saliva, a dry mouth, an increase of fever, and often a chill. The inflammation reaches its height in four or five days, and may abate or suppurate. The pus may drain into the mouth or rupture into it. As a sequel sepsis, fistula, destruction of the maxillary joint, necrosis of the bone, ulceration of the jugular vein with resultant hemorrhage or thrombosis, paralysis of the facial nerve, or a burrowing of pus into the middle ear or mediastinum may occur.

Acute Arthritis.—Acute arthritis as a complication of pneumonia has long been recognized, but was classed by the older writers as "rheumatism." It is now universally considered a true pneumococcic complication. Grisolle was the first to point out the similarity of this condition to the arthritis in pyemia and to suggest the same etiological factor as causative both of the pulmonary and the joint involvement. Arthritis may appear at any stage, involve one or more joints, and attack con-

jointly or individually the synovial membrane, bursæ, or joints. Cave has collected 30 cases of which 23 died. Two varieties are to be distinguished, the serous and the purulent. Fever, pain, local swelling, and redness are more marked in the latter variety, in fact in the former these may be very slight indeed. The onset of the joint invasion is occasionally heralded by chills and elevation of temperature. Among 22 cases collected by Brunner, 11 were monarticular, the shoulder being most often attacked. Recovery may take place, even in the suppurative form, without much local injury. Tournier and Courmont, however, believe that actual destruction of bony tissue occurs more frequently than is generally appreciated. Cave believes that all purulent cases should be treated by incision, flushing, and drainage. This form has a very heavy mortality, not from the local condition alone, but because it often bespeaks a severe infection. Six of Brunner's patients had acute endocarditis. Infection is usually by the blood stream in simple cases as well as in those in which mixed infection exists. It may, however, be carried by the lymphatics, as in the 29 cases of multiple, suppurative, pneumonic metastases studied by Bloch. Primary pneumococcus arthritis of the knee-joint has been reported.

Among 28,040 collected clinical cases, acute arthritis occurred in 150 (0.5 per cent.) and in 4 of 698 autopsies (0.57 per cent.). In 1903, Howard added a number to those previously collected and found the total number reported up to that date to be 72. Among 658 cases of pneumonia at the Johns Hopkins Hospital, Howard found 3 with pneumococcal arthritis.

An elaborate study of this condition has been made by Herrick.[1]

As further complications of pneumonia the following conditions may be mentioned: *Thyroiditis* ending in suppuration has been reported by Honsell, and by Lion and Bensaude. This seems to occur as a sequel and to terminate favorably after incision and drainage. *Suppurative orchitis* with a lethal termination, after a pneumonic relapse, has been recorded by Prioleau. *Bed-sores* occurred in 3 among 1552 collected cases. Preble noted 2 instances of *abscess* of the soft parts; in both pneumococci were found in the pus.

Pneumonia in Pregnancy.—*Frequency.*—Among 13,611 collected cases of pregnancy, there were 120 instances of pneumonia (0.8 per cent.). Jürgensen, in Vienna from 1858-70, among 1842 cases of pregnancy found 2.3 per cent. had pneumonia. Ransdell in the literature for twenty years could collect only 352 cases of coincident pregnancy and pneumonia. He believes that this rarity is to be explained by the lessened exposure of pregnant women to infection. Another reason is that pneumonia is more common in males, especially in hospitals, from which most statistics are gathered, and that the number of pregnant women in general hospitals is small. Ransdell found that of 190 patients in whom abortion occurred 70 died (36.7 per cent.), whereas of 118 who did not abort, only 12 died (10.7 per cent.). Abortion occurred in 58.8 per cent. of 352 cases. Of 144 patients with pneumonia in the first six months

[1] *American Journal of the Medical Sciences*, 1902, cxxiv, p. 12.

of pregnancy, 22.08 per cent. died, of those who aborted, 52.08 per cent. died. Of 164 cases in the last three months of pregnancy, 30.49 per cent. were fatal and 70.12 per cent. of those who aborted showed that the mortality as well as the frequency is higher during the latter part of gestation. Of 82 patients who died, 72 had aborted. The relation of abortion to the day of pneumonia was:

Day of disease	1	2	3	4	5	6	7	8	9	10	11+
Number of abortions	7	18	27	12	16	10	8	3	5	2	13

Of 52 patients who aborted before the third day, 21 died (40.38 per cent.) and of 69 who aborted after the third day, 19 died (27.53 per cent.). These figures indicate that if abortion does not occur in the first few days, the prognosis is better. It will also be noted that the third day is the most common one upon which abortion occurs. As to the infantile mortality, of 142 infants in whom the age of viability had been reached, 58 died (40.84 per cent.). Cases of transplacental infection from mother to offspring have been reported. Gangrene of the lower extremities in a pregnant woman suffering from pneumonia has been reported by Vetri.

The mortality from pneumonia is increased by pregnancy. More than half of the patients abort and when this occurs the death-rate is much higher. It is also higher during the later months of pregnancy. When death ensues, it is usually induced by a diminution in the quantity of hemoglobin, degeneration of the heart muscle, and overloading of the right heart after delivery.

Aufrecht has shown experimentally that in rabbits inoculated with pure cultures of pneumococcus, abortion occurred as the result of endometritis and was often followed by peritonitis. It is reasonable to assume that an analogous process occurs in the human being, and that the high mortality after abortion results from a pneumococcic endometritis.

Menstruation in pneumonia has been reported by Griesinger. In one, normal menstruation appeared on the third day of the disease and continued uneventfully. In another it appeared on the fourth day of the disease, ten days earlier than it was due. Beginning with the onset of the flow there was an evening remission of the temperature, instead of an exacerbation, *which proved to be the beginning of* a slow defervescence.

Occurrence with Other Infectious Diseases.—Pneumonia may occur as a complication of any of the infectious fevers. In *measles* lobular is much more common than lobar pneumonia. Very often it may be impossible to definitely determine with which of the two forms we have to deal. It is probable that the acute infection of the respiratory tract which occurs in measles opens a pathway for the entrance of the pneumococcus. Incipient pneumonia may be very closely simulated by atelectasis. "If loud bronchial breathing is heard over a dull area, a diagnosis of pneumonia is established; if this sign is absent, pneumonia may exist or the case may be one of atelectasis only" (T. V. Jürgensen). If dulness clears up more or less on deep inspiration, atelectasis is the prominent lesion. What has been said regarding measles applies with equal truth to *scarlet fever*, in which pneumonia is a very serious complica-

tion, especially when it appears during the course of a scarlatinal nephritis. Under these circumstances it not rarely causes œdema of the lungs, pulmonary abscess or empyema. Croupous pneumonia in the course of an attack of *diphtheria* is less common than in either of the above-mentioned diseases.

Pneumonia is the most frequent and the most serious complication of *influenza*. The literature on the subject is enormous, since different observers have taken quite opposite views regarding the etiology and pathology of the condition. The pneumonic process occurring in influenza may be caused by the bacillus of Pfeiffer, and thus be not a foreign complication but an integral part of the disease itself; or it may be brought about through the agency of the pneumococcus, the streptococcus or other organisms in combination or alone. Mixed infections in which both the specific organism of influenza and some other play a part are common. The pneumonia of influenza may be either lobar or lobular and the question as to which preponderates has caused unending discussion, the reason being that it is often extremely difficult to determine post mortem with which variety we are dealing, and at the bedside it is almost impossible to do so in the average case. Thus far it has not been demonstrated that the bacillus of Pfeiffer alone ever causes true lobar pneumonia. In the majority of cases this form of the disease is due to the diplococcus. Among the collected statistics of influenza complicated by pneumonia 97 cases were lobar as against 103 of the lobular variety.

When lobar pneumonia complicates influenza, chill at the onset is generally absent, but repeated chilly sensations may occur. The skin is more apt to be moist and severe sweats may occur even during the fastigium. Termination by lysis is very frequent, and defervescence is followed by greater prostration. Rusty sputum is often absent and the character of the temperature irregular. Post mortem, contiguous areas of the diseased lung may be in quite different stages of hepatization. Finkler lays stress upon the fact that frequently the only physical sign is percussion dulness over limited areas, no crepitant rales being audible at the beginning, although later on crepitus redux appears.

Lobar pneumonia as a complication of *malaria* is practically always of pneumococcic origin. True pneumonia due to the plasmodium of malaria is unknown, although the parasites may be demonstrable in the pneumonic consolidation. This complication is attended with a high mortality; Ascoli places the figures at from 60 to 78 per cent. Such pneumonias are often latent and overlooked; they may be very closely simulated by pulmonary congestion which is seen in some cases of pernicious malaria. The last-named condition may be manifested by dulness, rales, cough, dyspnœa, bloody expectoration, and even bronchial breathing. It generally occurs in the most dependent portions of the lungs. If true pneumonia is present the fever is apt to be continuous; if only congestion exists the temperature is of the intermittent variety characteristic of the malarial infection. Clinically, pneumonia complicating malaria assumes the asthenic type with prostration and marked nervous symptoms. Pneumonia is extremely frequent and fatal in individuals

suffering from chronic malarial cachexia. Complications are frequent, especially delayed resolution, with subsequent fibroid induration, and also pneumococcus septicemia.

In *typhus fever* lobar pneumonia is a very fatal complication, which is often unexpectedly discovered at autopsy.

Typhoid fever and pneumonia may occur coincidently or in rare instances the pulmonary consolidation may be due to the typhoid bacillus. Among 3514 collected cases of pneumonia there were 56 cases of typhoid fever, 24 of which died (42.8 per cent.). In 522 autopsies in pneumonia, the lesions of typhoid fever were found in 17, and in 891 autopsies in typhoid fever, pneumonia was found in 42 (18 per cent.). In 98 autopsies on cases of typhoid fever, at the Pennsylvania Hospital, Philadelphia, G. C. Robinson found bronchopneumonia in 29, and lobar pneumonia in 13 cases. In 12 of the latter, cultures from the consolidated areas showed pneumococci in 4, and stained preparations in 3 other cases; the *B. typhosus* in 1; the rest were pyogenic infections.

Lobar pneumonia occurring as a complication of typhoid fever is generally due to the pneumococcus, occasionally to the Friedländer organism or the typhoid bacillus. It appears most often during the latter part of the febrile period, rarely during convalescence or prolonged relapses. Pain, cough, and expectoration are often absent; the latter when present is apt to be hemorrhagic. The course of an attack of pneumonia in typhoid fever is generally protracted, resolution is delayed, and consolidation often imperfect. The mortality of pneumonia is about doubled by the coexistence of typhoid fever. According to E. Kraus the presence of pneumonia in typhoid fever may prevent the occurrence of the Widal reaction, and may cause the same to disappear after it has once been present. Typhoid fever inhibits the development of leukocytosis in pneumonia.

Bressel has reported lobar pneumonia following *gonorrhœa*, with colorless expectoration, lysis after the eighth day, the fever having previously been high. Resolution was complete by the eighteenth day. The sputum showed intracellular diplococci, Gram negative, and blood cultures the gonococcus.

Pneumonia as a complication of *heat prostration* occurred in 17 of 158 cases reported by Reid[1] (10.7 per cent.) with a mortality of nearly 53 per cent. It is more common in heatstroke than in heat exhaustion. The lower lobes are usually affected and the incubation varies from one to four days.

Diagnosis.—In typical cases probably no disease is more easy to diagnosticate than lobar pneumonia and such cases need not concern us here. Atypical cases may be confounded with acute tuberculous pneumonia, bronchopneumonia, especially in children, pulmonary congestion, pulmonary infarct, atelectasis, and most important of all, pleural effusions. In cases of central pneumonia the diagnosis may be in doubt for days.

Aside from the physical signs, the symptoms and a study of the temperature chart are factors which often aid. When laboratory facilities

[1] *Boston Medical and Surgical Journal*, 1912, vol. clxvii.

are available, blood cultures are the most positive means of diagnosis. The absence of leukocytosis speaks strongly against pneumonia except in very mild or very toxic cases. A history of chill at onset, especially if followed by chest pain, pyrexia, rusty sputum, or herpes, often settles the diagnosis. The mode of onset, the course of the fever, the pain in the chest, the cough, the peculiar expectoration, the dyspnœa, the abnormal pulse-respiration ratio, the peculiar character of the breathing—all of these have to be borne in mind in making a diagnosis in cases of obscure character. It must also be remembered that pneumonia is a disease of protean manifestations and that it often presents abnormalities of type; this is especially the case at the extremes of life, in drunkards, and in chronic disease. Whenever we have to deal with fever of uncertain origin, the lungs must be repeatedly and carefully examined. It is only by exercising unceasing vigilance that we can avoid having unsuspected pneumonias brought to our attention by the consultant or at autopsy. We should be particularly on our guard when we have to deal with a case of *influenza,* not only because this disease is frequently complicated by pneumonia, but also because when these two conditions go hand in hand the clinical picture of pneumonia is apt to be very atypical. When the possibility of pleural effusion arises it may be promptly settled by an exploratory puncture, although we must bear in mind that there may also be an underlying pneumonia. Subdiaphragmatic abscess may be excluded by the fluoroscope. The positive determination of a tuberculous process is often impossible until during convalescence, when tubercle bacilli or evidences of cavity formation may clear up the condition. It must be borne in mind that acute exacerbations of tuberculous processes which are too often considered as influenza with bronchopneumonia, may resolve to quite a remarkable extent. Cavity formation does of course not necessarily indicate tuberculosis; it may result from abscess, gangrene, or bronchietasis. In this connection the previous history of the patient is of great importance.

When the patient is not seen at the beginning, it is often extremely difficult to distinguish between pneumonia and *pleural effusion.* In the former disease the temperature is generally higher, leukocytosis more marked, and the sputum rusty, but it is not in the typical cases that doubt arises. Theoretically the physical signs of the two diseases should be quite different, but practically one finds cases of pleural effusion in which vocal fremitus, vocal resonance, and even bronchial breathing are present, or the breath sounds are only slightly modified. On the other hand in some cases of pneumonia we find only partial suppression of the vesicular murmur or feeble distant tubular breathing; increased fremitus and resonance are by no means always present. In both conditions we may have Skodaic resonance over the upper lobe, accompanied by exaggerated, harsh breath sounds. It may easily be seen that a differential diagnosis cannot be made upon any one symptom or sign, but upon a consideration of the whole picture. In doubtful cases the presence of pneumococci in the central parts of washed sputum often settles the diagnosis. Movable dulness does not exclude an underlying pneumonia, nor does the demonstration of liquid in the pleural cavity by means

of exploratory puncture, although both of these conditions may throw much light upon the question. Bronchial breathing may occur in pleural effusion as the result of pulmonary compression by the exudate, but in such cases it is usually best heard, sometimes only heard, over the middle or upper parts of the lung, and not at the base. In cases in which dulness appears suddenly and remains limited to the lower lobe the process is generally a pneumonic one. In making an exploratory puncture one should use a needle sufficiently long and of not too small a caliber, introducing it in the area of greatest dulness. Any signs of displacement of organs such as the heart, the liver or the spleen, speak in favor of pleural effusion. It should also be borne in mind that the heart may be displaced by consolidation of the lungs.

In pneumonia the affected side moves less than the sound side, but not to the same degree as in effusion. In percussing over an effusion, there is usually a greater degree of dulness and the sense of resistance is more marked. In pneumonia the area of dulness corresponds to the lobes of the lung, in pleural effusion the upper level of dulness follows an S-shaped curve, with the highest point in the axilla. In pleural effusion it is generally possible to demonstrate Grocco's sign—a triangular area of dulness over the opposite lung posteriorly, the apex being situated at the spinal column, at a height varying with the amount of the exudate, and the base at the lower limits of the pleural cavity.

Interlobar empyema may give signs and symptoms practically identical with those of pulmonary consolidation, being most often confused with delayed resolution or tuberculous infiltration. The reappearance of fever, malaise, weakness, leukocytosis, and pain after the disappearance of these following the crisis, should make us search very carefully for this condition. In these cases the exploratory needle and the *x*-rays are most useful. If no evidence of pus is found by the needle in the area of greatest dulness, we may at times demonstrate its presence by following up the neighboring regions which correspond to the septa of the individual lobes of the lung.

The differential diagnosis between incipient lobar pneumonia and acute *abdominal inflammations*, especially appendicitis, has been considered.

In the early stages it may be difficult to differentiate *typhoid fever* and *meningitis* from atypical forms of pneumonia.

Secondary pneumonias occurring in the course of other diseases are often overlooked. Even when suspected and sought for, the physical signs are not rarely of equivocal import, it being impossible to determine positively whether we are dealing with hypostatic congestion, œdema, infarct, a central pneumonia, or a bronchopneumonia. In all doubtful cases a disturbance of the normal respiration-pulse ratio—1 to 4 in adults—is very suggestive. In such cases every part of the chest should be very carefully examined, particular attention being given to the auscultatory phenomena high up in the axilla, above and below the clavicles, and under the scapulæ. No matter how carefully we make our examinations, we must expect from time to time to make a diagnosis of pneumonia without any positive physical signs. In children it occasionally happens that these do not become manifest until after the crisis.

Prognosis.—Wells has collected from the literature 465,400 cases of pneumonia with 94,826 deaths, a mortality of 20.4 per cent. It matters little whither we turn for our statistics, we are apt to find a mortality ranging from 20 to 25 per cent., taking any large series of cases as they come. Articles are constantly appearing, written by the enthusiastic advocates of certain lines of treatment, proclaiming a greatly diminished death-rate, supposedly the result of therapeutic success, but the mortality from pneumonia holds it own, unabated, in much the same proportion as that which our predecessors saw. The mortality in private practice is for obvious reasons distinctly lower than in hospitals.

According to the United States census for 1900 the death-rate from pneumonia per 100,000 of the population was highest in the registration cities of the registration States (233.1), lowest in the rural districts (135.9). It was much higher among the colored (349) than among the whites (184.8); higher for foreign whites (209.8) than native whites (176.9); also higher for native whites having one or both parents foreign (212.2) than those having native parents (155). There has been a slight increase of the death-rate in the cities since the census of 1890, and a decrease in the rural districts. "The death-rate from pneumonia was excessively high among those whose mothers were born in Italy (479.8), particularly in the cities (561.4). Among those whose mothers were born in other countries the rates were highest among those whose mothers were born in Ireland (257.5), and in Hungary and Bohemia (206.6). The rate was lower for the children of mothers born in the United States (142.8) than in any other class except those whose mothers were born in Canada (136.2)."

"The death-rates from pneumonia were highest among those under fifteen years of age (277.1), and at sixty-five years of age and over (805.4). At each age under sixty-five years the mortality from this disease was higher in males than in females; but at the age of sixty-five years and over the female mortality exceeded that of the males." In comparison with the figures of 1890, those of the 1900 census show a decreased mortality for those under sixty-five years of age; and an increase for those above this age. As regards the mortality according to *sex*, the statistics collected by the writer of 33,351 cases in males showed 6449 deaths (19.3 per cent.) and among 12,927 cases in females, 3431 deaths (26.9 per cent.). The total of 46,278 cases gave 21.1 per cent. mortality. The question as to whether lobar pneumonia is at present attended by a higher mortality than formerly has been much discussed without leading to any positive conclusions. There seems to be a general feeling among older practitioners that pneumonia is a more formidable disease now than of yore; a feeling which is apparently substantiated at least to a certain extent by the study of statistics.

Age.—The high mortality from pneumonia, especially in the aged and in those afflicted with chronic disease, is largely due to complications. This is well exemplified in Ashton and Landis' series of 991 cases from the Philadelphia General Hospital, in which the general mortality was 53 per cent. If the disease could be shorn of its complications,

the death-rate would be reduced more than one-half. Pneumonia is the great scavenger of the physically unfit.

Complications.—The earlier the onset of complications the less favorable the prognosis. The mortality in relation to complications in collected cases is as follows:

Complications.	Cases.	Mortality.
Pleural effusion	700	20.29
Empyema	74	39.19
Acute endocarditis	36	72.22
Chronic endocarditis	114	32.46
Acute pericarditis	125	64.00
Acute meningitis	33	93.93
Jaundice	344	15.7
Cirrhosis of liver	5	100.00
Peritonitis	7	100.00
Acute nephritis	116	65.52
Chronic nephritis	182	68.29
Acute arthritis	52	61.0
Emphysema	48	47.9
Pulmonary tuberculosis	215	57.9
Pregnancy	466	30.0
Hemiplegia	105	21.8

Repeated attacks of pneumonia seem to decrease the virulence. Baeck, Morhart, Pöhlmann and Stoertz all found a lower mortality among those individuals who had had previous attacks. Rychner's general mortality in 616 cases was 25.7 per cent.; whereas among those who had already suffered from the disease it was 22.7 per cent.; and among those who had had more than one attack it was 18 per cent.

Site.—The influence of the *site and extent of the lesions* is shown in the following tabulations based upon 4062 cases collected by Preble.

	Cases.	Deaths.	Per cent.
Right upper	448	90	20.0
Right middle	95	14	14.7
Right lower	1129	195	17.2
Right lung	336	141	42.0
Left upper	185	34	18.9
Left lower	1002	145	14.4
Left lung	309	84	27.1
Bilobar	251	91	36.2
Bilateral	307	110	35.5

The mortality according to the involvement (Sears and Larrabee) was:

	Cases.	Per cent.
One lobe	590	31.0
Two lobes	233	38.2
Three lobes	99	59.0
Four lobes	8	62.5
Five lobes	1	100.0
Double pneumonia	134	42.5

Temperature.—The effect of different *degrees of temperature and the pulse and respiration rate upon the mortality* is exemplified by Preble as follows. It will be noted that extremes of temperature are to be feared;

low or subnormal temperature often indicates lack of reactive power, whereas hyperpyrexia goes with an overwhelming toxemia.

Temperature and Mortality

	Cases.	Deaths.	Per cent.
Under 100°	17	6	35.2
102°	220	52	23.1
103°	302	83	27.4
104°	408	109	26.7
105°	386	99	26.0
106°	148	45	30.5
Over 106°	34	23	68.0

Pulse and Mortality

	Cases.	Deaths.	Per cent.
Under 100°	57	2	3.5
110°	123	7	5.7
120°	142	18	12.6
130°	288	62	21.5
140°	143	68	47.0
150°	125	74	59.0
Above 150°	83	64	77.0

Respiration and Mortality

	Cases.	Deaths.	Per cent.
Under 30	77	6	7.7
40	257	36	14.0
50	384	116	30.2
60	123	62	50.4
70	98	61	62.2
Above 70	23	14	65.6

To a certain extent the pulse-rate may act as a prognostic indication. Chatard in the Johns Hopkins Hospital found in cases with a pulse-rate below 125, a mortality of 14.9 per cent., a condition which occurred in one-half of the cases. With a pulse-rate above 125 the mortality was 49.4 per cent. If the rate increases and the pressure falls the outlook is not good (Hare).

Race.—W. Kolle, who studied an epidemic of pneumonia among the negroes at Kimberly, South Africa, found in over 1000 cases a mortality of 60 to 70 per cent. The high mortality in the negro is probably due to the same causes which have been considered under susceptibility. In addition we have the fact that in this country, at least, many of those classed as negroes are mulattoes, a stock which lacks resistance.

Alcoholism.—It has long been known that habitual drunkards have a very slim chance of recovery when attacked by pneumonia and it is noted also that the mortality among moderate drinkers is higher than among total abstainers. This fact is known to life insurance companies, as holding good for many diseases other than pneumonia. Delirium tremens complicating pneumonia is very frequently fatal. The statistics of a number of observers are collected in the following table:

MORTALITY

	Total abstainers. Per cent.	Moderate drinkers. Per cent.	Intemperates. Per cent.
Collective investigation report	10.4	17.4	42.8
H. H. Smith	20.0	32.0	70.0
Sears and Larrabee	25.0	26.7	45.5
Huss	...	...	25.0
Hadden, Mackenzie, and Ord	...	...	37.0
Townsend and Collidge	Combined	15.0	41.0
Norris	Combined	25.0	96.0
Aufrecht	Combined	24.0	45.3

Altitude.—Hoagland collected statistics of 6116 cases in cities approximately at the sea level and found a general mortality of 26.8 per cent. In 709 cases occurring in cities at an average altitude of 6580 feet the mortality was 22.1 per cent. Roberts in observations at altitudes of 200 to 300 and 3000 to 4000 feet had a slightly lower mortality in the latter. He found that heart complications were more frequent in the mountains, gastric and bowel troubles in the lowlands. Goodman in a study of 101 cases treated at the American Hospital at Mexico City found a mortality of 39.8 per cent. The disease was more frequent before the rainy season, and decreased during the rains and directly afterward. Connell agrees with Hoagland in a study of 261 cases at Leadville, Colorado, with a mortality of 26.4 per cent., and holds that it has been practically disproved that high altitudes increase the death-rate of pneumonia. Kieffer states that among 127 cases at Fort D. A. Russell, Wyoming, at an altitude of 6195 feet, during the last thirty-eight years, there were 20 deaths (15.74 per cent.). From 1868 to 1903 there was a mortality of 14.63 per cent. at Fort Russell, whereas in the whole U. S. Army during the same period there was a mortality of 15.61 per cent. Brewer, who has made a study of the subject based upon various United States Army statistics, arrives at practically the same conclusions.

Prophylaxis.—The infectious agent is transmitted from the diseased to the healthy individual chiefly through the sputum, but as the pneumococcus is found in the nasal and oral cavities of apparently healthy people, a dissemination from this source is also possible. Whether the organisms hitherto so considered shall prove to be identical, whether different strains of the same organism may develop essentially different characteristics, and, if so, through just what chemical or biological conditions their virulence may be diminished or enhanced, are questions which the bacteriologist must decide. The evidence points to the fact that the problem is an extremely complex one, and that a large number of factors may affect the virulence of the organism and influence the resistance of the individual. It would seem that certain people are predisposed to the disease, but in what this diminished resistance consists we are unable to say. The belief is no longer held that everyone carries the pneumococcus about with him in his oral or respiratory passages. Unquestionably, however, some healthy individuals do, especially those who come in contact with pneumonia patients, and chiefly during the winter months. Dissemination of the pneumococcus occurs in part by such individuals, in part by convalescents from the disease—bacilli

carriers, in part from individuals suffering from "colds," some of which are pneumococcic in nature.

It is unlikely that the increased prevalence of pneumonia is due to any general deterioration of resistive power, although it is believed that the growing frequency of cardiovascular degenerations plays an important role. This would not, however, explain the increase of pneumonia in children and young adults. Until these questions are more definitely settled from a bacteriological standpoint it would be useless to adopt the extreme measures of placarding houses and instituting a state of quarantine, advocated by some enthusiasts. On the other hand, all reasonable care should be exercised in the disinfection of sputum.

F. C. Woods, who has made a careful study of the viability of the pneumococcus, has arrived at the following conclusions:

A. The life of the pneumococcus in moist sputum is of considerable duration, the average period being less than two weeks unless the material is exposed to direct sunlight. But, as such sputum does not give off bacteria even when exposed to strong currents of air, it may be considered as innocuous except to persons handling clothes, bedding, etc., which have recently been contaminated. Under ordinary conditions this sputum dries in the course of a few hours or days. The dried masses retain their virulence for a long time and if deposited on the floor or on bedding may be powdered mechanically, and sweeping, dusting, or brushing the contaminated articles will distribute pneumococci in the air. Fortunately, the organisms do not remain long in suspension and die rapidly under the action of light and desiccation. In sunlight or diffuse daylight the bacteria in such powder die within an hour, and in about four hours if kept in the dark. The danger from infected sputum may be avoided by ample illumination and ventilation of the sick-room in order to destroy or dilute the bacteria and by the avoidance of dry sweeping or dusting. Articles which may be contaminated and which cannot be cleaned by cloths dampened with a suitable disinfectant should be removed from the patient's vicinity.

B. When a person suffering from a pneumococcus infection coughs, sneezes, expectorates, or talks, particles of sputum or saliva are expelled from the mouth, which may contain virulent pneumococci. Such particles remain suspended in the air for a number of hours if the ventilation of the room is not good. They may be inhaled by persons in the vicinity or deposited upon various articles in the room. Whether suspended in the air or dried on surrounding objects, they become harmless in a very short time, about an hour and a half being the extreme limit, while many of the pneumococci in the spray perish in a few minutes, especially if exposed to strong light.

The risk of infection from the pneumococcus is largely confined to those in direct contact with the patient.

Pneumococci have been isolated from the throats of 50 out of 80 normal individuals, from 66 out of 74 cases of lobar and lobular pneumonia, from 10 out of 15 common "colds," and from 14 out of 31 cases of miscellaneous disease. It is also probable that the virulence of the pneumococcus is somewhat higher in pneumonia than in "normal" cases,

although this is a very difficult matter to determine. Wells was able to demonstrate the pneumococcus in the respiratory passages, chiefly the throat, of 62 out of 135 individuals examined (45 per cent.). Certain other findings of the Medical Commission for the Investigation of Acute Respiratory Diseases should be noted, namely: (*a*) While a small number of individuals constantly harbor virulent strains of the pneumococci in their mouths, the majority of people do so only from time to time. (*b*) Individuals who come in contact with pneumonia patients harbor the microörganism in much greater proportions than those not so exposed. (*c*) Infection may be acquired from droplet infection, from dried sputum, and from actual contact with utensils which have been used by pneumonia patients. (*d*) Patients convalescent from pneumonia may carry virulent organisms in their respiratory passages for weeks or even months. (*e*) It is probable that infection may be acquired from some cases of ordinary "cold."

The *disinfection* of sputum is best accomplished by keeping a strong solution of lye or sodium hydrate in the sputum cup, the use of which should be enforced. The addition of bichloride of mercury, carbolic acid, and other disinfectants to sputum simply produces a coagulation of the peripheral mucus while the central part of the coagulum is protected. When isolation is possible, it should be carried out, especially in hospital wards and in rooms generally occupied by more than one member of a family. Patients enfeebled by age, renal and cardiovascular lesions or acute illness should be kept from contact with or even proximity to a patient with pneumonia. When association is unavoidable the bed should be screened, a procedure which would tend to minimize general aërial dissemination of microörganisms expelled in coughing. Those nursing pneumonia patients should be warned against needless handling of or proximity to the patient, and of touching their own face without careful disinfection of the hands. Aged and debilitated individuals and those who have once been attacked by pneumonia should preferably not be selected as nurses.

In regard to the general combating of the disease, something may be hoped for through the education of the public. It should be common knowledge that anything which tends to reduce the vitality—dissipation, loss of sleep, overwork, overworry, underfeeding, alcoholism, etc.—predisposes to an attack of pneumonia. Further, that exposure to cold draughts, or any chilling influence when overheated and perspiring, and especially when physically exhausted, directly invites infection. The foregoing statements by no means indicate coddling, overclothing or bad ventilation. It should be equally understood that the habituation of the body to cold air or water, when not carried to extremes, and when followed by a vigorous systemic reaction, is highly beneficial, as is also thorough ventilation and the habit of sleeping with open windows.

The duties of the municipal government should consist (*a*) in helping to disseminate knowledge of the above-mentioned character, (*b*) in enforcing regulations forbidding expectoration in public places, especially within doors, (*c*) in proper cleaning of the streets, a procedure which should always be preceded by thorough sprinkling, and performed only

at night, (*d*) in systematically disinfecting rooms in which patients with pneumonia have been lodged.

It is to be hoped that the future may bring forth some specific prophylactic measure, in the nature of a serum or an inoculation.

Treatment.—There is as yet no specific treatment for pneumonia. Antimony, iodides, mercury, veratrum viride, chloroform, iron, quinine, creosote, salicylates, digitalis, and a host of other drugs have proved valueless.[1] The results of *serum therapy* are likewise disappointing and yet there is some hope that in the future, in selected cases, larger doses than have hitherto been employed may prove of value (see Immunity). Vaccines and leukocytic extracts have not proved definitely beneficial.

Chemotherapy.—In the hope of finding a chemical specific for the pneumococcus, Morgenroth and his pupils[2] have reported some favorable results in experimental pneumococcus infections with the use of ethylhydrocuprein. Thus far, however, this substance has been used mainly on animals. Severe transient amblyopia was noted in 3 of 24 cases treated in human patients. The pneumococcus which survived the treatment produced strains which were resistant to the preparation.

The most important therapeutic indication in croupous pneumonia is to prevent or, if this is impossible, to modify the effects of toxemia, and to avert or treat complications. The animal infected with pneumococcus dies of toxic vasomotor paralysis, not of heart failure. If the vasomotors can be stimulated, the heart is perfectly capable of continuing its work. In the human being the problem is a somewhat different one, by virtue of the fact that pulmonary lesions (pneumonia) occur, which can only be produced in animals experimentally, if partial immunization has been established. Although in the human being we have this added mechanical factor to deal with, yet no one who has had an opportunity of studying many cases of croupous pneumonia can doubt the fact that most of the patients who die, do so as a result of toxemia and not as the result of mechanical factors increasing the work of the right heart, or from insufficient aëration of the blood. Several facts are frequently overlooked by the enthusiastic employers of different remedies, which it is worth while briefly to point out: (1) Pneumonia is a general systemic infection with local manifestations in the lung. In many cases the pulmonary lesion is only secondary both from the standpoint of infection and in its importance in producing a fatal termination. (2) Pneumonia is a definitely self-limited disease, which may occur in an abortive form by reason of decreased virulence on the part of the organism or increased resistance on the part of the individual. A specific effect might be very readily attributed to the action of a certain remedy which had been administered. (3) The mortality from pneumonia varies more or less in different years, epidemics, and localities. For obvious reasons, it varies greatly in small series of cases treated by the same methods, so that the individual observer is very apt to draw false conclusions. (4) Pneumonia is often due to mixed infection, or to entirely different

[1] See F. Rosenthal, *Zeit. f. Chemotherap.*, 1912, pt. 2, 1149.
[2] *Zeit. f. Immunitätsforschung. u. exp. Therap.*, December 12, 1912, vol. xv.

varieties of organisms, conditions which we are at present rarely able to positively or promptly determine. This factor probably in part accounts for the very diverse conclusions which have been arrived at by different observers who have employed different kinds of therapy. It is to be regretted that there seems to be a tendency from time to time to take up various old, well-tried, forgotten, and useless forms of medication. We have at present no specific for pneumonia, but each claimant for a specific treatment can, nevertheless, produce statistics to support his statements, providing the critic does not insist that the following considerations must qualify any presumed facts:

1. A number large enough to exclude the personal equation and other qualifying features must be analyzed.

2. The age, sex, social circumstances, and habits; the environment, character of epidemic, season of year, and circumstances of the life-history of the host as well as of the pneumococcus, and many other details, must be constant features in the groups of cases arranged for comparison. The pneumococcus may at one time be virulent, at another innocuous, or the host susceptible or relatively immune. Neither the host nor the organism are constant factors. Thus far in all literature there are no such comprehensive analyses. The thoughtful physician is compelled, therefore, to put aside all such vaunted specifics and subscribe to lines of treatment based upon principles derived from our knowledge of the action of the organism and the reaction of the host.

The action of the organism is that of an invasion or infection of the host inducing a general infection, a local inflammation, and a secondary toxemia. A favorable reaction of the host is seen in the ability to take care of the inflammation by physiological means, and to neutralize, eliminate, or withstand the effect of the toxins. As to the organism, after invasion or infection has taken place but little can be done by the therapeutist, save to perhaps limit the inflammation and increase resistance. To secure these we must lessen congestions which become points of lessened resistance and hence vulnerable to further invasions, we must ward off other microörganisms to prevent mixed infections, and we must prevent reinfections of the pneumococcus.

As to the host, we must aid every line of defence provided by nature. The nervous system, the circulation, the digestive apparatus, and the secretory organs must be carefully studied and their functional activity looked to. The aged, the debilitated, the sufferer from organic disease, should thus receive the help their enfeebled powers demand. In short, any attempt to defeat the inroads must be attained by a careful study of the host. It is on the patient, therefore, that most reliance must be placed for recovery and hence his resistance must be fortified and his powers of elimination aided. Fortunately many individuals evince enough power of defence, as manifested by good resistance and sufficient elimination. We know that death ensues in uncomplicated cases either from an overwhelming extent of the inflammation or from the toxemia. These factors serve, therefore, as the indications for treatment, and are in truth our conception of the morbid process which we have to combat. To do this successfully we must play with Nature's cards.

General Considerations.—When we are dealing with pneumonia, the scenes change rapidly and the passage of an hour or two may present an entirely different picture. The obvious lesson of this is that pneumonia patients should be watched carefully and seen by the attending physician at frequent intervals, especially during the latter part of the disease when judicious and well-timed medication may tide the patient over the crisis to recovery. Furthermore, the physician should always remember that there is no routine treatment, that each patient must be a law unto himself, and, finally, that it is the individual who needs treatment, not the disease. When clamorous relatives insist that something be done, it is far better to give a placebo than to risk the administration of any remedy whose physiological action is not clearly understood and whose employment is not definitely indicated. As Hare has very aptly stated, the physician "must be the watchman all the time, and the therapeutist only when treatment is actually needed." "All patients may be divided into three groups: those doomed to death by the malignancy of the infection, those that are but slightly ill by reason of mild infection, and those who are between the two extremes and need careful medical aid to accomplish recovery." For the first group no known treatment avails, for the second none is needed, but in the third therapeutics find a legitimate and fertile field.

The Inflammation.—This is the result of an infection, liable to increase in extent if the cause persists, atria of infection prevail, or local and general resistance falls below normal. Such local resistance is lessened if congestions are present, whether from cardiac, renal (toxic), or traumatic causes as we see in traumatic pneumonias. General resistance, on the other hand, is lowered by unhygienic conditions, by antecedent depressing influences, as disease or alcohol, and by the action of the toxin. We must consider the patient as an infected subject liable to reinfection from the same organism derived from without or resident within the mouth or fauces.

The patient should be scrupulously cleansed and then kept clean. The assailable mucous membranes should be cleaned and all abrasions sealed. The eyes, the nose and throat, and above all the mouth should have thorough and repeated cleansing with mild antiseptic lotions. The laryngitis, tracheitis, and bronchitis which frequently precede or accompany the infection should be treated by cold compresses and other hydrotherapeutic measures, by local counter-irritation, by the inhalation of proper medicated sprays or vapors, and by the usual remedies if they do not conflict with or replace medication that is necessary for the major infection. The discharges should be disinfected and destroyed at once.

Adequate *ventilation* of the sick-room is of the greatest importance. There is absolutely no danger of the patient catching cold, even when the windows are wide open. Thorough ventilation is of special importance if the room is small, if it is occupied by several people, or if there is a stove or light burning in it. In addition to being well-aired the bed-room should have as much sunlight as is compatible with the comfort of the patient. The temperature should never be

above 65° F., visitors and unnecessary attendants should be excluded, the use of the bed-pan enforced, and preferably a single bed should be chosen.

Aerotherapy.—Fresh air stimulates the heart and respiration. It supplies requisite oxygen, relieves "air hunger," promotes sleep, quiets restlessness and promotes digestion. As Jürgensen long since pointed out, "fever patients cannot catch cold." Franklin wrote, "Colds, so-called, are utterly independent of either wet or cold."

Method.—If possible, choose a sunny room, have the windows wide open, or the sashes taken out, regardless of weather or temperature. If there is dust or snow replace the window panes by cheese-cloth screens. The temperature of the room should preferably be below 65° F. Supply extra wraps for the nurses. Hot foot baths, followed by friction, are very beneficial. These and rectal injections can easily be given under the bedclothes. The patient's arms may be left outside the covers. Northrup pointedly says, "Do not make the patient breathe five times when three will accomplish the same effect. Give him air, fresh air, in unlimited amounts and constantly."

In the past few years, excellent results have been obtained by treating the patients in tents or on protected verandas. But little medication was given. It does not seem possible that anyone should cavil as to the advantages of such treatment; but it is necessary, before these plans can be adopted, to educate an unwilling public. A definite decrease in mortality in a large series of hospital cases treated in the open air has been demonstrated by the author.[1]

The *patient should wear* light woollen undergarments to prevent sudden changes of temperature and should never be clothed heavily enough to produce discomfort or profuse perspiration. Woollen and cotton jackets are still used by a few practitioners. The jacket poultice is, fortunately for the patient, a thing of the past, although of late it has unfortunately been supplanted to a slight extent by a somewhat similar procedure—that of applying various forms of pastes to the chest. The only advantage which such forms of treatment possess lies in their relief of pain, and this can be much more satisfactorily accomplished by other means. If the patient be outdoors in winter a rubber sheet or newspapers should be placed under the mattress and hot-water bags placed at the feet.

It is needless to say that all means which might disturb physiological processes must be guarded against. Improper feeding, undue exertion, excitement, and other disturbing influences must be corrected. When it is recalled that a large proportion of pulmonary pneumococcus infections are attended by infections of the colon, the influence of diet can be appreciated. The position of the patient should occasionally be changed; this, especially in the aged, tends to prevent hypostatic congestion. The bed should be comfortable so as to relax the muscles. The mattress should be firm enough to prevent sagging in the centre. Active friction and massage of the back and extremities facilitate the return of

[1] *American Journal of the Medical Sciences*, 1908, cxxxvi, p. 645.

venous blood to the heart and relieve stiff and aching muscles. Sleeping patients should not be disturbed for either food or medicines.

Bloodletting, Cupping, External Applications. — With the intention of controlling the extent of the inflammation, one of the measures above suggested may be employed. If the patient is robust and of plethoric type, and the local pain and chest oppression severe, the removal of a half-pint of blood by phlebotomy may yield good results. It has the sanction of many authorities, but the writer must confess he has but rarely resorted to it in the early stages, but has relied on other means to gain the same end. On the other hand, dry cupping is his practice (wet cups produce too many wounds). Cupping should not be limited to the supposed site of the inflammation, but the cups should be applied all over the lungs, front and back, to the number of twenty or thirty. It should be done early and repeated every six or eight hours as long as pain persists, the dyspnœa or oppression continues, or the respiration rate rises. After cupping, the pain may further be relieved by thorough *strapping of the chest.* The fixation induced is of immense relief. External applications of sinapisms, liniments, and ointments are of value for the friction required and the psychic effect induced. Dry cold in the form of the ice-bag or the coil helps to relieve pain and perhaps limits congestion. The fact that it does induce comfort and is often grateful to the patient is a strong argument in its favor. Many do not like cold or are depressed by it. Dry heat, by hot-water bags or flannels, gives comfort to many, and for the aged and debilitated may be useful, although never curative.

Hydrotherapy.—Greater confidence can be placed in hydrotherapeutic measures than in other forms of local treatment. These have the advantage of inducing peripheral stimulation and therefore also combating the toxemia, for which general hydrotherapeutic measures also avail. We have the cold sponging, the cold compresses, and the mustard foot bath at our command. The *effect of baths* is to calm the nervous system, deepen respiration, aid expectoration, reduce fever, and stimulate the heart and vascular system.

Baruch points out that *in children* under eight years, the tub bath, 90° F., with friction, is of value, used for six to ten minutes when the temperature is above 102° F., especially if there be nervous symptoms. It is well never to use water below 80° F. for children. If there are symptoms of circulatory failure—dyspnœa, cyanosis, or other alarming manifestations—the child should be put in the tub with water at 100° F. up to the navel, and two to four basins of water (at 75° F. to 65° F.) poured over the shoulders. Then he should be dried with considerable friction. Jacobi advises "cold baths, or packs when the temperature is high, but most patients do quite well with sponging or friction with wet towels. The latter plan is both refrigerant and stimulant."

For *adults* the baths are too disturbing, although the temperature yields more readily than in typhoid fever. In severe cases with threatened collapse, however, a bath of 100° F. to the waist, and water 75° to 65° F. poured over the shoulders, is of value. It may be employed also when stupor is marked. Sponging is performed primarily to stimulate the nervous system, to increase blood pressure and blood flow,

only secondarily for the reduction of temperature. It should be used more or less routinely and not dependently upon any specified amount of fever. The windows should be temporarily closed.

This treatment is especially efficacious in toning up the vasomotor system. It also furthers the elimination of toxin (Roque and Weil have shown that the toxicity of the urine is increased by it).

Cardiac Depressants and Hypnotics.—Measures which lower the blood pressure should not be employed. The severe rigor at the onset and the marked pain in the side contribute to shock the patient more or less. One plan, therefore, is to give a full dose of morphine, preferably hypodermically. Repeated small doses are not as safe or as beneficial. Patients over fifty should be examined for renal disease before morphine is given, and to those with nephritis it should be given sparingly if at all. The morphine counteracts the shock, induces sleep, and relieves pain. Dover's powder is a favorite remedy for pain, cough, and restlessness. All opiates should be discontinued as soon as the indication for their employment has disappeared.

Laxatives and Diuretics.—In addition we have diuretics and laxatives which have a place in the therapeutics of pneumonia. *Laxatives* may be employed in the first period. The patient often has a heavily furred tongue, anorexia, and constipation. Small doses of calomel (gr. $\frac{1}{8}$, gm. 0.008) or mercury with chalk may be given hourly until a grain is taken. It is often advised to give calomel in one large dose (5 to 10 gr., 0.3 to 0.6 gm.). With or without calomel, Rochelle salts or saline cathartic waters may be given and repeated according to the indications. There are some who prefer to give robust subjects the compound cathartic pill or elaterium (gr. $\frac{1}{4}$ to $\frac{1}{6}$, gm. 0.016). The liquor ammonii acetatis may be given every second hour.

Diuretics.—These are in agreement with the other measures, as they favor elimination. Water is the best diuretic. From 4 to 8 ounces should be given hourly. Pneumonia patients are often stuporous, and although they will drink water when offered will not ask for it of their own accord. Liquids should therefore be frequently offered. A glass of lemonade, to which one or two teaspoonfuls of potassium bitartrate has been added, makes an excellent and generally acceptable diuretic draught. Lemonade or orangeade or iced tea may be employed. The salts of potassium are useful diuretics. Unless there are complications it is not wise to give digitalis or squill. If the urine is scanty, saline solution may be given by the bowel or subcutaneously.

Toxemia.—This manifests itself first by an increased stimulation of the nervous system—wakefulness, excitability, delirium, etc. Later, the results of overstimulation become evident in enfeeblement, depression, hebetude, stupor, or coma. The management of toxemia consists in reënforcing resistance, increasing elimination, and counteracting the effects of the toxins. No antitoxin thus far obtained can be relied upon for therapeutic relief. Resistance to the toxins can be secured by aerotherapy, hydrotherapy, careful feeding, and, when required, moderate stimulation.

One of the most successful methods of treating toxemia is that of saline

enteroclysis given continuously over variable periods of time as each case may demand. Intravenous injection may be employed if rapid action is desired, but this should not be employed without preliminary venesection if cardiac dilatation is marked. In patients with renal disease it is quite possible that the sodium chloride may become an actual danger, as the normal ionic balance may be upset sufficiently to cause death *per se*. As a general rule there is much less danger from enteroclysis than from venous transfusion. In such cases a 2 per cent. solution of glucose may be substituted, although practically the author has never seen anything but good results from saline enteroclysis.

Elimination may be further induced by stimulants, as those employed to directly counteract the toxins, or by remedies such as caffeine or diuretin. It is usually not necessary to continue their use more than a few days. Coffee and tea should be used for this purpose if they do not make the patient nervous. In cases of endocarditis with failing compensation, digitalis may be tried, especially hypodermically or intramuscularly in the form of digipuratum (gr. $1\frac{1}{2}$, gm. 0.1), or digalen (0.5 cc.); or strophanthin (Boehringer) (1 mg.) may be substituted. As a general rule drugs of the digitalis group are useless in fevers. This fact long known and repeatedly pointed out is constantly ignored.

Stimulants should not be used until needed, and then used without stint.

Much has been written in commendation and in deprecation of the use of *alcohol* in pneumonia. Certainly its employment is falling more and more into disuse. The facts seem to be as follows: It diminishes the opsonic power of the blood. It tends to diminish the glycogen content of the liver, and this substance has been shown to increase the resistance of rabbits to infection. It lowers blood pressure in both normal and pneumococcic animals. It tends to empty the arteries and fill the veins. Except for a brief initial stimulation its effect is depressing. It diminishes the work done by the heart per minute. Collected statistics of patients treated with and without alcohol show a lower mortality when it is withheld (Hay), and even in chronic drunkards immediate withdrawal is better than temporizing administration (Galli, Hernung).

Ammonia may be used as a stimulant, either constantly, at repeated intervals, or intermittently. Its place is limited to stimulation or when bronchitis complicates the pneumonia. The aromatic spirit of ammonia may be given regularly or when symptoms demand a rapid diffusible stimulant. It may be used to combat flatulence or acidity. It may be of much service if there is palpitation or dyspnœa in paroxysms. The routine administration of expectorants is an obsolete practice unless a severe bronchitis be a complicating factor. *Camphor* in oil is given hypodermically when there is adynamia with cerebral depression and cardiac exhaustion. It is fugacious in its action and is generally given too late to accomplish beneficial results. Strychnine, hypodermically, should be given, especially if the pulse is rapid, feeble, and dicrotic and the respirations hurried. It is not to be used in a routine manner.

The Crisis.—Caution and watchfulness must be enjoined at the expected time of and in the event of the crisis. The greatest care must be taken

not to allow undue exertion, as sitting up in bed or straining at stool. Food must be administered in the recumbent posture and stimulants employed freely, usually in the diffusible form. Hot bottles or external heat in other forms should be applied and hot drinks given. Strychnine, and adrenalin or, if there be excessive sweating, atropine may be relied on to counteract the undue shock.

The Skin.—The usual care must be extended to the skin, and especially in the pneumonia secondary to diabetes and chronic nephritis. The herpes requires anodyne dusting powders, as camphor, morphine and zinc oxide, sedative lotions, as camphor water or boracic acid in alcohol, or ointments, such as oxide of zinc with or without morphine or cocaine.

The Nervous System.—The ice-cap or coil to the head is of much service. The ear must be kept cleansed and any commencing infection thwarted by the application of ice, and by perforation of the ear drum or trephining of the mastoid as indicated. The delirium of alcoholism demands more active stimulation, which should be begun early. Postcritical delirium requires food and stimulants and may be aided by hyoscyamus, hyoscine hydrobromide or scopolamine. Large doses of bromides with trional may bring the desired sleep. Opium and morphine are usually not of service. The wet drip sheet may be required and is often effectual. Cerebral symptoms—insomnia, delirium, etc.— may result from insufficient intestinal evacuation, gastric distension, or renal insufficiency.

The Cardiovascular System.—If the heart is healthy a lethal termination is generally due to *vasomotor paralysis*. The blood accumulates in the dilated splanchnic vessels, and the vital contents and the other organs are insufficiently oxygenated. The blood is gradually drawn from the periphery and continues to be pumped with a steadily increasing pulse-rate into the great stagnant splanchnic pool. Intracardiac pressure falls, the cardiac and respiratory centres, as well as the coronary arteries themselves, are progressively less well supplied with blood, until at length complete collapse occurs. This picture of pathological physiology is clinically manifested by a fall of blood pressure, an increased pulse rate, pallor, sudation, tympanites, restlessness, delirium, cardiac arrhythmia, stupor, and coma.

The most efficient treatment is fresh air, cold sponging, mustard foot baths, saline transfusion and the hypodermic or intravenous administration of epinephrin. Strychnine, atropine, and caffeine are of value, but digitalis and its congeners are rarely of benefit unless cardiac dilatation be an associated feature. The nitrites although temporarily improving the pulse are absolutely contra-indicated. This statement holds good for all phases of pneumonia.

Dilatation of the right heart while frequently present to a slight degree sometimes becomes the chief factor in serious cases. This is mainly the case if toxemia is great, the pulmonary involvement extensive, and the heart already weakened by renal, arterial, pulmonary, or valvular disease. It is manifested by cyanosis, venous distension, tachypnœa, enfeeblement of the pulmonic second sound, increased pulse-rate, muffling of the first sound, enlargement of cardiac dulness to the right, diminished urinary secretion, hepatic enlargement, and pulmonary œdema.

The most effective treatment is associated with cardiac stimulation administered hypodermically or intravenously (digipuratum, digalen, strophanthin). From 8 to 24 ounces of blood should be removed and the procedure repeated if necessary. Dry cupping, two or three times daily, often gives a measure of relief. Aromatic spirit of ammonia, caffeine, or camphorated oil hypodermically may be used. Cardiac or vasomotor weakness should be promptly treated during the early manifestations; in the later stages but little can be accomplished. But, on the other hand, nothing can be more reprehensible than routine stimulation. A great nicety of judgment and one which can only be acquired by wide experience is required to decide just when and how much to stimulate. No absolute rules can be laid down but certainly it is better to err on the side of understimulation. The greatest benefit which the fresh air treatment achieves lies in the fact that patients become less toxic, so that in the average case no stimulation whatever is required. The calcium salts (lactate grs. xv, gm. 1) have been suggested by Brunton as a cardiac stimulant in pneumonia, because they are said to neutralize the toxins of albumoses and peptones, to counter-balance the sodium chloride retention—ionic equilibrium being reëstablished, and because of their direct action on the heart. Vagus action is abolished by loss of calcium and reëstablished by its renewal.

Very similar symptoms and physical signs may result from a *pericardial effusion.* In such a case the withdrawal of a few ounces of fluid from the pericardium may yield great relief. A diagnosis from cardiac dilatation is not always easy. An antecedent, gradually disappearing pericardial friction sound is often a valuable criterion, and for this purpose a careful daily examination of the precordium should be made. If such a friction be discovered an ice-bag should be applied. This is often useful even when there is no pericardial involvement. The application of cold to the precordium slows the heart and thus steadies and strengthens its action. Purulent effusions call for surgical intervention. Such pus collections generally occur after the crisis.

The author has never seen any benefit follow the use of *oxygen inhalations,* although theoretically they should be of benefit in cases of extensive pulmonary involvement. They probably do no harm, but it should not be forgotten that in concentrations of over 70 per cent. oxygen inhalations may cause pneumonia in healthy lungs.[1]

The Lungs.—If bronchitis is marked expectorants must be used. Aromatic spirit of ammonia may be given. Large pleural effusions are to be aspirated and empyemas treated surgically as soon after the crisis, if it occurs, as possible.

The Gastro-intestinal Tract.—The question of *diet* is of the greatest importance. Nutrition should be kept up to the highest point. Formerly, as the result of misapplied treatment, it was not unusual for death to occur during convalescence, as the French put it "mort guéri." The food should be selected for its nutritional value, the ease of assimilation being

[1] Alfred Adams, The Effects of Atmospheres Enriched with Oxygen on Living Organisms, *Biochem. Jour.*, 1912, vol. vi, p. 307.

equally considered. The ideal food, therefore, is milk in some form. This may be given plain, peptonized, diluted with lime water, or with some cereal added, or in the form of koumiss or junket. Gelatinous foods, broths, or beef juice may be alternated with milk, but it should not be forgotten that, with the exception of the last of these, the nutritious value is much less than that of milk. Sugar and starches sometimes produce fermentation, and must therefore be given with caution. Raw eggs, custards, scraped beef, and ice-cream are allowable. Eggs may make up a large portion of the diet. Strong black coffee may be administered when heart failure or stupor calls for stimulation. All food should be given at regular intervals, varying from two to four hours, according to the amount taken. Sleeping patients should not be aroused for nourishment, but stupor must not be confounded with restful sleep. The juice of oranges, grapes, lemons, and shaddock are often relished. A very palatable diuretic beverage may be prepared by adding a teaspoonful of cream of tartar to a pint of boiling water, squeezing in the juice of half a lemon and serving when cold. The sucking of cracked ice is much relished and beneficial. Effervescent beverages are better omitted, especially if there is a tendency to flatulent distension. The various forms of predigested foods may be given, but it should be borne in mind that nearly all of them contain alcohol and relatively little nutriment. The same general rules apply in the case of *children*. If, as is sometimes the case, an infant is too ill to nurse, the mother's milk should be withdrawn by means of a breast pump and fed to the child a few drops at a time with a teaspoon. With older children, fed upon cows' milk or artificial food, it is generally advisable to dilute the food.

Although the caloric value of the diet is of less importance in pneumonia than in a prolonged wasting infection, it must not therefore be neglected. In the crisis itself, to say nothing of the complications which may follow, the patient may require every particle of vital energy which his system is capable of furnishing. Each patient should receive as a minimum the equivalent in diet of 33 calories per kilo. The average man would therefore require about 2300 kg.

Not only must the total quantity be regulated but the relative proportions as well. Thus in case of the proteins, not only are the daily requisites fixed, but Nature has no methods of storing up excesses as is the case with sugars and fats. Hence the eliminative organs are overworked if too large quantities be administered. On the other hand, protein repairs the wear and tear of the bodily tissues and must therefore be supplied. The amount generally required ranges between 60 and 80 grams. The necessary proportion of the three food elements is generally given as: carbohydrate 400 to 500 grams, protein 100 grams, hydrocarbon 50 grams.

In connection with the diet we have to consider the administration of *sodium chloride*. During an attack of pneumonia the chlorides are generally greatly diminished, often entirely absent from the urine for a number of days. This salt retention is general, not local. There is no one point of accumulation, although the formation of the exudate is one factor. This retention is not due to failure of absorption nor to an

increased amount of salt in the blood. It would seem rational, therefore, to suppose that these salts are required for some purpose by the economy. Some authorities have taken this fact as an indication for the administration of chlorides—without any beneficial results, it must be admitted, but also without any deleterious ones.

Incessant vomiting may be relieved by ice compresses or mustard plasters. The diet should be much restricted and gastric sedatives employed. Colitis is a serious complication. Correction of diet is the first indication, careful high irrigation of the large bowel the second. Salt solution or boric acid solution may be used. Tympanites may ensue because of fermentation or of toxic paresis. For the former, restriction of the diet is necessary. The latter is an indication to increase stimulation, and especially strychnine. The salicylate or nitrate of eserine, physostigmine (gr. $\frac{1}{100}$ to $\frac{1}{40}$, gm. 0.00075) may be of value, given every four hours hypodermically. Intramuscular injections of aseptic ergot are sometimes useful. Alum enemata, the insertion of a rectal tube, abdominal stupes, alternate hot and cold compresses, or gentle abdominal massage may be employed. Jaundice is not likely to require special treatment.

The Genito-urinary Tract.—Nephritis does not require special medication. Pneumonia occurring in a subject of chronic nephritis requires more alertness and more prompt measures to combat the toxemia. Hot packs may be required.

Convalescence.—The management of convalescence depends on the complications and mixed infections that have arisen. If the toxemia has been great, the patient should be enjoined from work, either mental or physical, for a long time. No half-way measures should be advised. If cardiac complications occurred, the usual exercises and baths for this condition would be of service and timely. Pulmonary complications may require a change to a milder climate or to the sea.

Delayed Resolution.—The treatment of this condition must be directed toward improving the patient's general health and nutrition. A constant and liberal supply of fresh air must be supplied; pulmonary gymnastics may prove beneficial. Among the most generally applied measures are the external application of blisters, iodine, and the actual cautery, accompanied by the internal administration of the iodides. Some very convincing results have been reported by Edsall and Pemberton,[1] who applied *x*-rays to a number of these cases. These rays exert a powerful influence upon metabolism, perhaps through their action upon various ferments. The possibility of a tuberculous process should be excluded before using the *x*-rays.

We should be very chary about adopting the suggestion which has been made of employing the *x*-rays therapeutically while the disease is in the active stages. The chief danger at such times lies in the toxemia, and by stimulating metabolic processes we should be running a grave risk of swamping the economy with a larger quantity of poisons than can be eliminated.

[1] *American Journal of the Medical Sciences*, February, 1907, p. 286.

CHAPTER IV

TUBERCULOSIS: HISTORY AND ETIOLOGY

By EDWARD R. BALDWIN, M.D.

HISTORY[1]

In Antiquity.—Pulmonary tuberculosis, consumption, or phthisis has existed from very remote times. It transcends all other maladies in the total number of its victims and the cost to society in civilized countries. Tuberculosis was a disease familiar to the most ancient civilizations, judging from the cuneiform inscriptions on tablets found in Babylonian remains, which represent the earliest known human records. Whether or not it existed in the most primitive state of man is a question without present hope of solution.

Hippocrates (B.C. 460–376) was the first to give an intelligent description of phthisis, although empyema and "phyma," abscess of the lung, were included in his classification. Otherwise his portrayal of the symptoms of consumption was unsurpassed for many centuries, and his works became classic. The Hippocratic school believed in the curability of phthisis in all stages, and the benefits of a change of residence. Contagion was mentioned by Isocrates. Aristotle, also a contemporary of Hippocrates, notes that it was a general belief among the Greeks of his day that phthisis was contagious. Celsus (B.C. 30) wrote of the disease in three forms: atrophy, cachexia, and ulceration. Aretaeus (A.D. 50) gave a very clear description of the disease and differentiated it from empyema. He believed in the efficacy of sea voyages and country air. Pliny also lauded pine forests for their healing powers.

Galen (A.D. 131–201) considered the disease an ulceration which should be treated by measures designed to dry the secretion. He therefore sent patients to the high land of Phrygia. In other details the conceptions of the disease held by Galen were like those of Hippocrates; nor was any further light shed upon the nature of consumption for 1400 years, when anatomical study began.

From Sylvius to Laennec.—The celebrated Sylvius (1695) was the first to indicate the connection between tuberculous nodules and phthisis. He regarded these nodules as enlarged lymph glands in the lung, analogous to scrofula, and on the scrofulous constitution depended the inheritance of phthisis. He gave a careful description of the symptoms

[1] The writer is indebted for much of the history and chronology in this chapter to the works of Waldenburg, Die Tuberkulose, 1869; also that of Predöhl, Die Geschichte der Tuberkulose, 1888; and Johne, Die Geschichte der Tuberkulose des Rindes, etc., 1883.

and believed in contagion. Morton (1689), whose celebrated book was widely known among English physicians, brought the tubercle prominently to attention as the true cause of phthisis; he also believed in heredity and contagion. Morgagni (1682–1771) was uncertain that tubercles and glands were identical, and thought that phthisis could originate from other things; he regarded it as extremely infectious, and refrained from doing autopsies on consumptives.

The noted Sydenham (1624–1689), Boerhaave (1668–1738), and his pupils, Auenbrugger and Van Swieten, wrote of phthisis without adding anything of importance to the previous conceptions of its nature, but largely represented the views of Hippocrates, Galen, Sylvius, and Morton. The teachings of Benjamin Rush exerted a powerful influence on American medicine of Revolutionary times. He wrote *Thoughts upon the Causes and Cure of Pulmonary Consumption* (1783), in which it was regarded as a disease of debility and tubercles, the result of hypersecretion from the bronchial vessels. He believed in contagion at first, but doubted it in later life. His treatment was vigorously antiphlogistic: bleeding, purging, etc., in the acute or febrile stages, and supporting measures in the debilitated stages.[1] Most noteworthy is the work of Bayle (1803), who is justly named as the founder of correct teaching about tuberculosis. He studied miliary tubercles in all stages, and laid great stress on their varying degrees of opacity; earlier gray tubercles were "granulations" of quite different character.

From Laennec to Villemin.—Laennec (1819), whose work soon followed Bayle's, consummated and simplified the knowledge thus far gained. He recognized the unity of all phthisis as tuberculosis, and scrofula as tuberculosis of lymph glands; his ideas in general as to causation and infection were distinctly modern, and his descriptions of the tubercle and its transformation toward ulceration are unexcelled. Most valuable of all was his gift of the art of auscultation. No genius like that of Laennec so far anticipated his own day. The teachings of Bayle and Laennec were not accepted without opposition.

During this period America was represented but meagerly in original investigation until 1834, when Samuel Morton, of Philadelphia, published the first pathological studies on consumption. He was a student of Laennec, and his conclusions as to the nature of tubercles were fairly accurate; they were ascribed to altered secretion and not to inflammation. Morton's work on *Pulmonary Consumption* found much favor in America, and included excellent therapeutic advice as to open-air life and exercise.

Inoculation Experiments.—English, American, and German physicians accepted the probability of infection under special conditions, but the strongest opinions were held by the Latin races, among whom the disease was said to be more virulent. The influence of Valsalva and Morgagni was certainly most potent in causing fear in Italy. The first recorded inoculations were by Kortum (1789), which, like some of those

[1] H. B. Jacobs has presented an excellent account of Benjamin Rush and other American writers on tuberculosis in the *Johns Hopkins Hosp. Bull.*, 1902, xiii.

of his successors, were fortunately unsuccessful, since they were partly upon human beings, including themselves. The strife over the question of the danger of inoculation of scrofula with vaccination led to these first attempts. Klencke (1843) first announced successful intravenous inoculation of a rabbit. Great attention was bestowed upon the microscopic and chemical investigations during the first half of the nineteenth century and hypotheses multiplied about tuberculosis

Virchow (1847–50) classed scrofula and tuberculosis entirely apart, restricting the latter term to the miliary form and considering it a form of lymphoma due to an unknown diathesis; caseation was a non-specific process. Hence the idea of unity in tuberculous diseases received a serious rebuff in spite of the important discovery by Buhl (1857) that miliary tubercles were most often associated with preëxisting caseous foci, from which he thought the specific poison originated. The microscopic studies brought out valuable data, but withal much confusion.

Period from Villemin to Koch.—Villemin presented his important communication in December, 1865, "On the Cause and Nature of Tuberculosis and the Inoculation of the Same from Man to Rabbit." His conclusions were positive: "(1) Tuberculosis is a specific affection. (2) It has its origin in an inoculable agent. (3) The inoculation from man to rabbits is very successful. (4) Tuberculosis pertains, therefore, to the virulent diseases, and should be classed with variola, scarlatina, syphilis, or, better still, with glanders." He covered a wide field in his inoculations, employing fragments of lung tubercle, sputum, blood, scrofulous gland, and perlsucht or bovine tubercle, with positive results in nearly all cases. Villemin's conclusions excited widespread discussion and control experimentation, for such far-reaching statements commanded attention. A new era of science was founded about the same time by Pasteur, and had he not become engaged in other investigations it is permissible to think that his genius might have crowned the work of Villemin by anticipating Koch's discovery by several years.

Every conceivable method of inoculation in control experiments was used. Besides tuberculous products there were those of cancer, syphilis, typhoid, pneumonia, and suppurations; inorganic substances, such as cinnabar, glass, silica, coal-dust; organic material, filter paper, hair, cork powder, lycopodium seeds, croton oil, moulds, etc. Coincidently exhaustive histological studies were carried out and their results discussed with fervor. The majority of experimenters corroborated Villemin's results in part, but much weight was brought against his conclusions about the specificity of tubercles by those who obtained tubercle-like nodules from indifferent substances. The old idea of inflammation dominated many, who regarded tuberculosis as simply a reaction to many kinds of irritation.

The contest over the specificity of the giant cell, the importance of which was emphasized by Langhans (1868), was settled in the negative. Tubercles were studied in all the tissues hitherto unassociated with the conception of tuberculosis, as fungous joints, carious bones, and lupus, by Koster (1873) and Friedländer (1873). The development and spread of miliary tubercles were traced to venous infection by Weigert (1879–82).

The pathway of infection was already inferred by the many feeding and inhalation experiments, so that with the rapidly developing investigation of bacteria caused by Pasteur's discoveries search was being made for a specific living organism. E. Klebs (1877) was the first to observe actual transference of the virus by artificial culture on egg albumen through several generations before inoculation, but he did not succeed in recognizing the bacillus; instead he found a motile organism, the *Monas tuberculosum*, which he presumed to be the *contagium vivum*. Aufrecht (1881) and Baumgarten (1882), independent of Koch, described bacilli in the centre of the tubercles, which, owing to lack of culture and staining methods, were not positively identified as the infective agents. Thus the actual achievement was due to Robert Koch, who was a health officer in an obscure German town.

Koch's demonstration of the causative relation of the tubercle bacillus to tuberculosis was so complete that but little of importance has been added since. The first attempts at staining the organism were by means of methylene blue made faintly alkaline by caustic potash and with vesuvin as a contrast stain. With these stains Koch was able to demonstrate the bacillus in all kinds of tuberculous tissues of man and animals, except when the tubercles were calcareous or otherwise healed. Moreover, by cultures on blood serum through several generations and reinoculation the proof was made complete, and the long dispute about the nature of scrofulous gland and skin diseases, as well as various pneumonias, was finally settled. The logical application of the knowledge, so conclusive and simple as to the infectiousness of sputum, has required many years to become general. Much aid was given in this direction by the investigations of Cornet (1888) on the presence of bacilli in dust.

The subsequent announcement of tuberculin as a probable cure (1890), the more recent discussion as to the relationship between human and bovine tuberculosis excited by Koch (1901), the vaccination studies, and the still more radical views introduced by von Behring (1902) as to the source, time, and pathway of infection, constitute periods in the recent history of tuberculosis to which may be added the rapid extension of preventive measures and the sanatorium movement.

The stimulus thus given to researches in tuberculosis has been notable. On the twenty-fifth anniversary of the discovery of the tubercle bacillus, the Robert Koch Foundation for the Prevention of Tuberculosis was inaugurated under the direction of Professor Koch at Berlin in May, 1908. Its object is to continue his scientific studies. The death of Robert Koch occurred at the age of sixty-seven years, on May 27, 1910.

ETIOLOGY

Statistics.—General.—The prevalence of tuberculosis is universal; no other diseases is so widespread or produces so much poverty and long-continued distress. From one-seventh to one-tenth of all deaths and an enormous proportion of invalidism are due to it. In the United States of America the population at the last census (1910) was 92,000,000.

The number of deaths from tuberculosis in the Registration Area, comprising 58 per cent. of the population, was 86,309 for 1910, being 160.3 per 100,000. A low estimate of the total mortality from all forms of this disease in 1910 reaches 145,000. In Prussia the total for 1910 was 60,479, or 15.29 per 10,000 living persons.[1]

The important factors influencing the mortality tables are density of population, occupation, social condition, race, color, and sex. Occupation and social condition appear to have the most intimate relation to the ratio of mortality. Stonecutters, cigarmakers, and plasterers head the list, with about half the deaths in these occupations; farmers and persons under the best social conditions have less than one-eighth due to tuberculosis. The greatest mortality from tuberculosis is between the fifteenth and forty-fourth year of life, when it causes one-third of all the deaths occurring during that period. The months of greatest mortality are March, April, and May, when other respiratory diseases are at their height.

The economic loss from tuberculosis is enormous even with a low valuation placed upon an individual life.[2] Fisher[3] has presented most elaborate and useful computations of the loss from invalidity and death in tuberculosis. Using $700 as the basis of an average year's earnings, he estimates the net cost for an individual as $4000. In the year 1906 there were approximately 138,000 deaths, which cost when all the factors were calculated $1,100,000,000. Fisher also estimated on the basis of the rate of mortality in 1908 that 5,000,000 of those living at that date would ultimately die of tuberculosis.

Geographical Distribution.—Tuberculosis is prevalent at all latitudes and altitudes and in all climates. It is most frequent in temperate zones and lowlands, and is rare in the elevated plateaux and Arctic regions. The influence of occupation and density of population explains to a large extent the differences in its incidence rather than geographical location alone. There seems, nevertheless, to be a distinctly protective influence in the climates of arid regions, and especially in elevated, invigorating climates, as Colorado, Mexico, and the Alps. The tropical countries furnish no statistics as to the frequency of tuberculosis, but it is said to be less common than in temperate regions, although more rapid in its course.

Race.—The question of varying susceptibility in different races has been much discussed and is closely connected with that of inherited or acquired immunity. It is certain that the aboriginal and uncivilized peoples easily acquire it in a rapidly fatal form, even when their conditions of living are favorable. Notable among such races are the American Indians, Negroes, and Hawaiian Islanders. The half-breeds and mulattoes are especially liable to the disease, and it has usually

[1] Medizinalstatische Nachrichten, 3 jg., 1911–1912, Heft ii, Berlin, 1911.

[2] In the United States 84.8 per cent. of the tuberculosis mortality (1910) in the Registration Area was classified as "tuberculosis of the lungs." A. Newsholme gives 69 per cent. for England and Wales (1903), and Cornet 81.3 per cent. for the German Empire (1896 to 1900).

[3] *Sixth International Congress on Tuberculosis*, 1908, vol. iii; *Report on National Vitality*, Bulletin No. 30, 1909, National Conservation Commission.

followed the advent of the white races among uncivilized natives. Benjamin Rush stated that the disease was unknown in America among the Indians in their natural wild state, but the early New England physicians mention its prevalence among the natives in their day. The recent emigration to Alaska has been followed by the decimation of the Indians from various diseases, especially measles and tuberculosis in acute forms. It is reasonable to suppose that the greater virulence is in part due to greater susceptibility of tissue, though undeniably the chief factors are filthy habits, poverty, and predisposing diseases.

Decrease of Tuberculosis.—One of the most encouraging and instructive facts is the remarkable decrease in the death rate in civilized countries during the last fifteen years. It is at once a confirmation of the value of hygienic measures and one of the obvious benefits of improved conditions of life for the laboring classes in large cities. From being the greatest scourge during the nineteenth century, when Good thought it no exaggeration to estimate that one-fourth of the population of Europe died of consumption, it is becoming so greatly lessened that in twenty-five years, from 1885 to 1911, the rate for Prussia fell one-half, or from 3.1 to 1.53 per 1000 living. The same is true of England, where a decrease of one-half has taken place among males and two-thirds among females in forty years. In the United States there was a decrease of 54.9 per 100,000 living between 1890 and 1900, the rate being 254.4 and 109.5 respectively. In the decade from 1900 to 1910 the rate for the United States Registration Area has declined from 196.9 to 160.3, an estimated saving of 27,000 lives. This decrease is principally in the large cities, New York being the most conspicuous by a lessening of 40 per cent. in sixteen years (4.06 to 2.68 per 1000, 1887 to 1902).

A. Newsholme,[1] who has made exhaustive studies, finds that the factors accompanying the decrease are very complex, and that much of the decrease occurred before the discovery of the tubercle bacillus and the increased hospital and sanatorium care; the latter, however, he considers the most important factor: "Segregation in general institutions is the only factor which has varied constantly with the phthisis death-rate in the countries that have been examined. It must therefore be regarded as having exerted a more powerful influence on the prevention of phthisis than any of the other factors of which none has varied constantly with the phthisis death-rate."

To summarize the facts: (*a*) The death-rate from tuberculosis has decreased in the places where special attention has been given to the hygienic control of the disease from one-seventh of all deaths in 1890 to one-tenth and less in 1910. (*b*) The general mortality from all diseases registered has declined from 19.6 to 15 per 1000 in the United States between 1890 and 1910, principally because of the lessened rates from tuberculosis and children's diseases. It is significant that the development of sanitation has been rapid during this decade.

Zoological Distribution.—*Animals in Natural State.*—Tuberculosis is practically unknown in animals or birds in the wild state or among

[1] *Journal of Hygiene*, 1906, vol. vi, p. 374.

those who have never been confined or brought in contact with domesticated species. It is quite otherwise with animals in menageries and zoölogical gardens. Monkeys and apes are the chief sufferers; rabbits and guinea-pigs rarely acquire it spontaneously. Instances are known of the disease in the giraffe, antelope, zebra, lion, tiger, jaguar, panther, fox, jackal, tapir, etc. Wild birds in aviaries are likewise subject to avian tuberculosis, but, excepting parrots, rarely acquire the mammalian type. Occasionally, carnivorous birds like the hawk, eagle, owl, and stork have been found tuberculous, as well as water fowl—ducks, geese, swans, and cranes. Spontaneous tuberculosis in reptiles, fishes, and other cold-blooded animals has been long regarded as a possibility, though rare. Inoculation experiments with mammalian tubercle bacilli also seemed to confirm this opinion, but more careful recent investigations (Weber and Taute, 1903) have revealed that the disease in these animals is probably a form of pseudotuberculosis produced by a saprophytic bacillus.

Domestic Animals.—All domesticated animals and birds are known to be liable to tuberculosis, but the frequency is greatest in dairy cattle. The proportion is estimated as from 10 to 15 per cent. in America, but is much greater in the British Isles and Europe, where as high as 30 per cent. has been discovered by inspection and the tuberculin test. It is said to be unknown on the islands of Jersey and Guernsey; also in Japan, where a certain insusceptibility appears to exist among the native stock (Kitasato). The greater incidence of tuberculosis among highly bred cattle is significant of the effect of the more careful housing, and hence greater opportunity for contagion. The increasing use of the tuberculin test has revealed an enormous prevalence of latent tuberculosis in apparently healthy cows. Next in frequency to dairy cattle, hogs are most subject to this disease and suffer chiefly from the bovine type of tubercle, from which fact it is evident that they obtain the infection from cattle, both by association and in food, especially milk. The practice of feeding offal obtained from abattoirs is a frequent source of infection.

In the United States reports of inspections nearly 1.5 per cent. are said to be found tuberculous, but it reaches 7.5 per cent. in some localities, and it is even more frequent in Europe.[1] The disease in hogs is often acute, but also presents a chronic lymphatic type; hence the name "scrofula," from *scrofa*, a sow.

Sheep are seldom affected, there being but 0.003 per cent. in 37,000,000 inspections, many of which were probably instances of pseudotuberculosis. In Prussia 0.76 per cent. tuberculous sheep were reported in 1904.[2] Horses, goats, and asses are likewise relatively immune to spontaneous infection, but European veterinarians have reported several cases among goats, doubtless of bovine origin. Camels are occasionally tuberculous. Dogs and cats, like other carnivora, are quite insusceptible, yet several hundred cases have been recorded, and the disease is

[1] J. R. Mohler and H. J. Washburn: "Tuberculosis of Hogs," *Annual Report of United States Bureau of Animal Industry*, 1907.

[2] R. Mayer: "*Die Schaf-Tuberculose*," Inaug. Diss., 1908, Freiburg.

alleged to have been produced by contact with consumptives, in most instances from swallowing or inhaling sputum. Kittens are quite easily infected from milk containing tubercle bacilli (Nocard). Among rodents, rats and mice are highly resistant to experimental tuberculosis, and are not spontaneously diseased.

Avian or fowl tuberculosis is most frequent among chickens. It seems to be common in Europe, but relatively infrequent in America. Pigeons, turkeys, ducks, geese, and pheasants have it to some extent, by reason of their habit of feeding with chickens whose infected excreta contaminates the food. Cases among canaries and other small pets are recorded, but more often parrots have obtained the disease from human sputum by accidental inoculation. Many reported cases of avian tuberculosis have doubtless been confused with pseudotuberculous infections.

Bacillus Tuberculosis.—Morphology.—The tubercle bacillus is a minute, colorless rod, and according to the classical description of Koch, has a slightly bent shape, with generally uniform contour and slightly rounded ends. It is very variable in length and somewhat so in thickness.

Staining Properties.—The most striking peculiarity, which distinguishes it from most other bacteria, is the power to hold aniline dyes in spite of long exposure to acids and alcohol. The acid-alcohol resistance is due to the peculiar waxy nature of the bacillus, which substance by extraction with alcohol and ether may be entirely removed, and with it the specific staining reaction. Ordinary basic aniline dyes stain this organism with difficulty.

Pleomorphism and Classification.—The many modifications in form and size which can be produced by varying the growth conditions have led bacteriologists to class the tubercle bacillus as a parasitic fungus capable of a higher order of development than ordinary bacteria. Under favoring conditions for saprophytic growth, bizarre forms with lateral branches and long filaments with club-shaped ends or swellings and vacuoles may appear, of a striking similarity to actinomyces. This pleomorphism of tubercle bacilli is rarely found in the true parasitic condition of growth, *i. e.*, in the tissues of animals, but may be found in sputum. These branched forms and other morphological variations are most often found in cultures of fowl tuberculosis, but also in those of human and bovine types (Wolbach and Ernst).

In consideration of these similarities to other fungi, bacteriologists are inclined to place the tubercle bacillus in a class intermediate between the bacteria and streptothrices; hence the name proposed by Coppen-Jones, "tuberculomyces," and by Marpmann, "mycobacterium tuberculosis."

Spore Formation and Involution Forms.—Koch described highly refracting bodies in the tubercle bacillus, most of which took no stain, but some were intensely stained and unusually resistant to acids. He considered both to be evidences of spore formation, but the unstained segments familiarly known in many sputum bacilli have since been recognized as vacuoles or breaks in the protoplasm. Globular, deeply staining bodies are, however, more nearly allied to spores, though not

possessing the heat-resisting powers of other known spores. They often occupy one end or the middle of a bacillus, and the deeply stained balls with a faintly stained rod attached, which is usually of lesser diameter, are very characteristic for old or inactive cultures. They are also seen in considerable numbers in sputum from chronic cases. All the bacilli may show them, and the conclusion is justified that they are resting forms even if not strictly signs of sporulation. The vacuolation is due to shrinkage and loss of protoplasm, which then loses more or less of the acid resistance in decolorized preparations of old or dead bacilli. Young living cultures may occasionally present vacuolation when cultivated on brain media (Wolbach and Ernst). In the main, however, young forms do not have many vacuoles in ordinary cultures, nor in sputum from acutely progressive disease. They may readily be produced in an artificial way by extraction with solvents. Fragments ("Splitter") of tubercle bacilli have been described by C. Spengler,[1] and Hans Much[2] described granular forms not always associated with rods which could be stained by a combined method with methylene blue and Gram's iodine, but not with the usual carbol-fuchsin stain. They appear to be resistant forms which are most often associated with tuberculous lesions, in which the rod forms are scarce, owing to strong lytic action or unfavorable growth conditions. They are capable of reproducing rod forms by inoculation or culture.

Varieties.—At the present time it may be stated that there are four fairly distinct types of strictly infectious tubercle bacilli: The human, bovine, avian, and reptilian or piscine. Besides these there are certain saprophytic bacilli which are probably distinctly related to the preceding and properly classed as pseudotuberculosis bacilli. Many observations in the past tended to show that these varieties were capable of comparatively rapid transformation from one into another, and originated from a common source or stock. This, in fact, was the original belief of Koch at the time of his first inoculation experiments, but the studies on the morphology and virulence of mammalian bacilli by Theobald Smith (1898) and those of Lartigau, Ravenel, Schutz, and others raised doubts as to their identity and to disputes as to the interinoculability of the human and bovine types. The constancy of these differences led Koch to a negative position as to the danger of "perlsucht" or bovine tubercle bacilli for man, and to a diligent study of the whole question since the discussion at the British Congress for Tuberculosis (1901). Out of much strife the truth seems to have emerged in favor of an intermediate position between the standpoint of those who hold the belief in strictly distinct varieties and those who favor an absolute unity for all. While the German Imperial Commission[3] appointed to study the question has reported in favor of radical distinctions as held by Theobald Smith, the United States Bureau of Animal Industry[4] found that the types of tubercle bacilli are very inconstant. The exhaustive

[1] *Zeitsch. f. Hyg. u. Infektionskrank.*, 1905, Band xlix.
[2] *Beitr. z. Klinik. d. Tuberk.*, 1907, Band viii.
[3] *Tuberculose Arbeiten aus dem Kaiserliche Gesundheitsamte*, vols. i, iii, x, xi, xii.
[4] *United States Bureau of Animal Industry*, Bulletin No. 52, i to iii.

studies of the British Royal Commission[1] for the past ten years in the final summary confirm the main conclusions of the German commission. They found intermediate types of virulence, especially from cases of lupus, which appeared to belong to both human and bovine varieties, but of lower infectivity. They also met with some human types of high virulence. Therefore, while the main point of contention, namely, that the bovine type of bacilli is capable of infecting human beings to a considerable degree, is now considered settled affirmatively, there is yet sufficient reason for a broad distinction between the human and bovine types, and still more between them and the avian and reptilian bacilli. It is therefore important to note the points of difference possessed by the most characteristic individuals in each class.

Human Type.—This form grows more readily on all media, produces increased acidity in culture broth (Smith), and is less virulent for small and large herbivora than the bovine. It rarely infects carnivora, and yet more rarely fowls, birds, and reptiles.

Bovine Type.—In comparison with the longer human and avian types the outline is more irregular and often oval and plump, with blunt ends; the staining is less uniform, but vacuolation is not so evident. The growth is slower in cultures, though ultimately not different in appearance from the human, and produces an alkaline reaction in culture broth (Smith). It is infectious for all mammals so far tested by inoculation experiments, and is more virulent for them than the human type.

Avian Type.—The bacillus of chicken tuberculosis is similar to the human type in general appearances, but shows pleomorphism more frequently. Growth is rapid on all media, and is distinguished by a moist, creamy consistence seldom seen in the others. It thrives at a higher temperature (43° C.) and produces an alkaline reaction in broth cultures (Bang). It is highly infectious for barnyard fowls, but less so for pigeons and carnivorous birds. Very few animals are susceptible and guinea-pigs are nearly immune. Rabbits may easily be infected. Mice, rats, and pigs have been successfully inoculated, and have been found spontaneously diseased (Rabinowitsch), but the larger animals are quite refractory; it was, however, found in a monkey by Rabinowitsch. Cases have also been reported in which the avian bacillus has been found in human sputum and in cattle and horses (Johne and Frothingham, Nocard), but they lack complete proof of their origin from avian sources.

Reptilian and Piscine Type.—It has been customary to include among tubercle bacilli certain varieties which grow readily at low temperatures (20° to 25° C.), and are found in fishes and cold-blooded animals such as frogs, snakes, lizards, and turtles. These are now relegated to a class by themselves, and are only infectious to reptiles and fishes under unknown conditions, but not to mammals and birds so far as known. They belong to the class of pseudotubercle bacilli,

[1] *Final Report of the (British) Royal Commission, etc.*, 1911, Part ii, Appendix, vol. i to iii.

which can grow in nature as saprophytes and cannot be ascribed to an alteration of mammalian or avian types under natural conditions.

Pseudotubercle Bacilli.—During recent years an increasing number (between 40 and 50) of acid-proof bacilli have been encountered which strongly resemble true tubercle bacilli in morphology and staining properties, but more often show actinomyces-like forms. The most important are the milk and hay bacilli of Moeller and the butter bacilli of Rabinowitsch, Petri, and others. They are generally rather thicker and less acid-proof than true tubercle bacilli, and all grow more rapidly and at low temperatures. Cultures of the various milk, pseudobovine, and grass bacilli, of which many varieties have been described, are similar in so many features that it is very likely that they are closely related if not identical in origin.

The smegma group forms another series of acid-proof bacilli which are of more importance in causing confusion in the diagnosis of tuberculosis.

None of this class can claim parasitic importance for mammals, yet inoculation may produce localized tubercles which soon disappear without caseation in guinea-pigs and rabbits, thereby indicating that they may simply be the result of a foreign-body irritation.

No evidence has been forthcoming that any spontaneous disease results from these organisms except in fishes and reptiles (Dubard, Friedmann, and Küster[1]). They have been a source of error in some of the earlier researches in connection with milk and butter; nor can they be neglected in connection with the diagnosis of human tuberculosis, especially of the genito-urinary and intestinal tracts. Koch showed that specific tuberculosis-agglutinating serum caused agglutination of grass bacilli and precipitation of their culture fluid. Extracts of smegma and grass bacilli are capable of producing tuberculin reactions (Krause[2]). Irimescu[3] prepared a "paratuberculin" from acid-proof bacilli. Biological relationship with the true tubercle bacillus may therefore be assumed.

Differentiation.—*By Staining.*—All forms of tubercle bacilli stain deeply with acid-fuchsin-phenol or aniline-water, but retain the stain with varying tenacity under treatment with acids and alcohol. In general, the pseudobacilli decolorize more easily. In doubtful cases such tests are unreliable, and inoculation should be done.

By Culture.—The differences in reaction produced in broth cultures are noted elsewhere. Theobald Smith and Bang consider that the human can be differentiated from the bovine and avian types by this.

Biology.—The tubercle bacillus is a facultative parasite, requiring conditions for its growth outside of animals which do not exist in nature so far as known. Its multiplication is relatively slow, being far outstripped by most bacteria, and this fact alone would render its existence difficult except in pure culture, since the associated organisms would soon exhaust the soil. The tubercle bacillus is non-motile and grows

[1] One case of enteritis in a cow is reported by Borgeaud as due to them. Cf. *Bakt.*, vol. xxxix, Ref.

[2] A. K. Krause: *Studies from Saranac Laboratory*, 1912.

[3] *Zeit. f. innere Med.*, 27 Jr., p. 26.

more rapidly and more luxuriantly the less its virulence. The property of pleomorphism has led some to regard it as an abortive form of a fungus, unable to complete its cycle of development as a parasite.

Transformations into Other Types and Variations in Virulence.—Conclusive proof is thus far wanting of an actual or permanent transformation of one type into another by passage through animals or by culture. Much interest was excited in this subject by Koch's announcement of the non-identity of human and bovine tuberculosis in 1901, and it was still a subject of difference of opinion at the Paris Congress of 1905. On the whole, the evidence is against such a change, since the published reports of the British and German Commissions, although an increase of virulence of the supposedly human type for goats and cattle is apparently shown by the inoculations of v. Behring, Pearson, Ravenel, and Eber, and especially by Dammann and Mussemeier and Karlinski. Against these are the negative results of Theobald Smith, Kossel, Weber, Heuss, and Neufeld. Others represent the opinion that transition forms exist between the two types (v. Behring, Dorset, Fibiger and Jensen, Eber, Rabinowitsch, L. and M.). Practical difficulties stood in the way of an easy solution of the question, and also the determinations of inherent differences of virulent grade of the human type for man by inoculation into rabbits, guinea-pigs, and calves. Instances of such altered virulence are attributed to the presence of a mixture of both human and bovine types in several cases studied by the British and German Commissions. That these differences exist is apparent in the varying clinical course of tuberculosis in certain families in which the source of infection may be assumed to be the same for each member. Some are mild and chronic, others acute and rapidly progressive; nor can assumed differences in susceptibility always account for this.

From the extensive work of C. Fränkel on the question of differences in virulence, there would seem to be considerable variation between cultures from human sources in this respect.

Cultivation.—Difficulties beset the cultivation of the mammalian bacillus from the tissues of the diseased animal, and it grows reluctantly at first on most media. The first evidence of growth to the eye is a group of minute dull or glistening points after five to ten days, rarely less than eight days. The increase is slow, but in three weeks the surface is covered either by a thin, dull pellicle or small, mealy grains, isolated or crowding together, which form slowly heaping-up masses or wrinkles. The multiplication of tubercle bacilli is presumably by end fission, which results in peculiar S-shaped curls or tapering, curved tufts in beginning growths; these are composed of masses of parallel rods and are caused by the longitudinal crowding of the young bacilli.

Freshly isolated cultures from animal tissues on serum or egg tubes are usually shorter, more homogeneously stained, and uniform in size than further transfers on other media. The tubercle bacillus will not grow directly from the animal tissue in a liquid medium, but the thin pellicles which spread over the condensation water of serum cultures, or scales carefully lifted from the solid surface, are transferred easily, floated upon broth, and grow luxuriantly as a wrinkled crust over its

surface. The broth underneath remains clear, which fact provides a rough test for the absence of contamination.

Isolating Pure Cultures.—Koch succeeded first in isolating pure cultures by the use of coagulated blood serum, and it remains today one of the best sources of fresh cultures. Dorset's egg medium is probably the simplest and easiest method for isolating pure cultures from tissues. It is made by breaking fresh, cleansed eggs into a sterile flask and thoroughly mixing the yolk and white, after which the mass is strained through sterile cheesecloth and distributed into sterile tubes. No neutralization is required, and the tubes may be coagulated at once at a temperature of 78° C. inclined in a blood-serum oven, or, better, heated three successive days at 70° C. Before use a little sterile normal salt solution or water is best added to the bottom of each tube to preserve moisture.

After scorching the surface of a fresh tuberculous spleen, lung, or other organ with a hot scalpel or spatula, bits of the subjacent cheesy or otherwise tuberculous tissue are torn out and squeezed between the broad blades of forceps or sterile glass slides, from which they are quickly transferred by a platinum loop or spatula to the surface of the egg and gently rubbed about on the middle of the slant. Tearing the surface of the medium is to be avoided, and to be favorable the surface should be fragile and elastic.

From Sputum.—This may be done very successfully by means of Hesse's agar[1] if a fresh sputum rich in bacilli is at hand, or still easier, by the use of antiformin sedimentation of the sputum and directly planting the sediment upon egg or serum media. The contaminating bacteria in sputum are completely destroyed by shaking five parts of sputum to one of antiformin. The latter consists of equal parts of sodium hydrate and Javelle water, and must be washed out of the sediment before transference to the culture tubes to insure growth.

By Inoculation.—For this guinea-pigs are best and should receive the sputum under the skin of the abdomen. The animal should be killed in three or four weeks—not permitted to die, since terminal infections are likely to defeat attempts to cultivate the tubercle bacillus.

Culture Media.—A great variety of culture media are available for the tubercle bacillus. As stated, blood serum is most useful in isolating fresh, virulent cultures; it is best prepared in Loeffler's mixture, but not coagulated as hard as for diphtheria cultures. Dog, sheep, and beef serum are to be preferred in the order named; as already noted, eggs are the best substitute. For further growth 3 to 5 per cent. glycerin-agar is useful. All kinds of broths and vegetables besides synthetic media are very successfully used. Cultures for diagnostic tuberculin are now usually made on beef broth with 2.5 per cent. glycerin.

The notable peculiarity about culture media for the tubercle bacillus is the high degree of acidity which is favorable for their growth.

Duration of Life.—Tubercle bacilli in cultures retain vitality at least six months if preserved from drying. They may die in three weeks

[1] The formula is: Heyden's Nährstoff, 5 grams; NaCl, 5 grams; glycerin, 30 grams; agar, 10 grams; sol. Na_2Co_3 (cryst.), 28.6 per cent., 5 cc.; water, 1000 cc. Other albumose foods, such as somatose or nutrose, are said to be equally good.

when not so protected, or at least cannot easily be revived by transplantation. Avian cultures retain life much longer, according to Maffucci, who recovered cultures and produced infection after two years. A more important question is the vitality of the human bacillus in the (clinically healed) diseased foci in which the bacilli are encysted and dormant. The observations on this subject are unsatisfactory. Cornet infers that their life is short in the tissues because of the difficulty in growing cultures from old tubercles. On the other hand is the fact of apparent latency for years, during which time all evidence of growth has ceased, yet recurrence of the disease may ultimately occur in the immediate vicinity of the former focus; this is especially manifest in lupus. The early inoculation experiments by Baumgarten with "latent" tubercles, and those of Kurlow and Lubarsch with healed tubercles indicated the persistence of virulence in old caseous tubercles not yet calcified or only partly calcareous.

L. Rabinowitsch[1] found 15 out of 34 chalky human lymph glands virulent, while Piettre[2] obtained positive inoculations in 55 per cent. of chalky tubercles in cattle. The granules of Much are possibly the most resistant parts of the bacillus and retain vitality a long time. Weiss[3] found only granules in the calcified lymph glands of eight children.

Schroeder and Cotton's results from inoculations of virulent human bacilli into calves, which produced localized subcutaneous abscesses, are significant of considerable latency. Guinea-pigs were readily infected from the pus after periods of five months to one and one-half years. Positive results from inoculations have been obtained from lymphoid tissue in which no signs of tubercles were discovered (Loomis, Weichselbaum and Bartel, and Rosenberger). How long these bacilli were actually latent or had suspended growth is, of course, uncertain, but experiments by Weichselbaum and Bartel, Perez, and Manfredi and Frisco on rabbits tend to show that their vitality is limited to but a few months, when the inoculations remain latent without further growth. The general result of inoculation experiments indicates three to six months as the period during which the bacillus may live in the tissues *without multiplying*, although clinical observations are difficult to harmonize with this statement. Weakening of virulence has been noted by Manfredi and Frisco, but Harbitz was unable to detect any differences in this respect in lymph glands from children of different ages.

Presence of Tubercle Bacilli Outside the Body.—The human sputum being the chief source of the tubercle bacillus, it is naturally present in the dust of infected rooms, besides being attached to the furnishings, walls, and floors of such rooms. It is rarely found in the open except in the dust of crowded streets, and the enormous dilution of the air and water renders it very infrequent in nature. The customary disposition of urine and feces renders these sources of small account. The presence of bovine bacilli is practically limited to the stables of cattle and hogs with open (ulcerated) tuberculosis, and these are uncommon. The

[1] *Zeitschr. f. Tuberk.*, 1910, Band xv.
[2] Baumgarten's *Jahresbericht*, 1909, Band xxv.
[3] *Münch. med. Woch.*, 1909, Band lvi.

exhaled breath is free from bacilli, but they may escape in all other excretions and be secreted in milk. Altogether, the opportunities for tubercle bacilli outside the body are directly dependent upon the degree of cleanliness used in the disposition of the sputum, urine, and feces, and their presence in milk from tuberculous cows. Cornet made it clear in his investigations that the presence of bacilli was only to be assumed in places frequented by careless consumptives.

Powers of Resistance.—*Heat.*—The lowest fatal temperature for the tubercle bacillus is 55° C. (131° F.) moist heat, acting for a period of six hours (Cornet). Dry heat is borne to 100° C. for an hour without killing the bacillus, according to Schill and Fischer in experiments with dried sputum. The thermal death-point for tubercle bacilli in milk is of great practical importance, and many experiments have been made which determined that from 60° C. (140° F.) to 75° C. (167° F.) was sufficient if continued for one hour. More recently, Theobald Smith, Hesse, Bang, and others have shown that the usual method of pasteurizing milk at about 60° C. to 65° C. in an open vessel or bottle is insufficient to kill them, since they come to the top in the scum and thus remain cooler than the underlying liquid. Therefore, if pasteurization is desired the milk should be stirred or placed in a closed vessel and heated at least twenty minutes to 65° C. (149° F.). Bang concluded that 85° C., the Danish legal requirement, was a sufficient temperature to sterilize the dairy refuse fed to calves and hogs.

Cold.—The tubercle bacillus is not destroyed by any degree of cold, but alternations of thawing and freezing are destructive to its virulence.

Drying.—Dry bacilli from cultures may lose virulence in three weeks, but the more important question as to the vitality of tubercle bacilli in naturally dried sputum involves such varying conditions that the preservation of infective power depends upon the size and thickness of the sputum mass, its quality, its place of deposit with reference to the character of the surface, and, most important of all, its exposure to light, heat, and air. When sputum of tenacious character is dried in large masses the bacilli are shut out from the air in the hard, glue-like crusts; and in a dark, cool place, such as a basement room or the corridor of many city dwellings, the maximum period of vitality may be assumed to be from six to eight months; this is the estimated limit given by Cornet as the result of his own and numerous other researches. A valuable series of studies by Flügge and his associates in recent years has revised to some extent the conclusions of Cornet as to the virulence of dry sputum in dust which is capable of floating in the air. The ingenious experiments of Kirstein with sprayed and dried sputum brought into the form of dust indicate but a short lifetime for bacilli thus exposed to air and in diffused daylight. The following were his conclusions: Dust from library books was found infectious after eight but not after fourteen days; powdered sputum alone, after four but not after seven days; lint from sputum-smeared clothing, after five but not after ten days; sputum mixed with street dust, after three but not after eight days.

Water.—Experiments by Chantemesse and Widal showed that the *Bacillus tuberculosis* could live in sterilized water from the Seine from

fifty to seventy days. Galtier preserved them four months in water. The influence of light and decomposition hasten their death under natural conditions in water.

Putrefaction.—Putrefaction of sputum and tuberculous animal tissues usually destroys the tubercle bacillus within a few days (Baumgarten and Falk, de Toma, Schill, and Fischer). It is dependent, however, on the nature of the process and how rapidly it takes place whether the products of decomposition are harmful to the bacillus or not. Galtier was able to infect animals after two months with putrid spleen and lung. This question is of interest in relation to the persistence of virulence in the diseased cadavers and excreta of man and animals because of the possible danger of transmission by means of infected earth, insects, etc. Cadeac and Mallet found buried tuberculous lungs virulent after five months, but Klein not after seven weeks. Gärtner concluded that tubercle bacilli could survive for months in feces.

Gastric Juice.—The tubercle bacillus can be destroyed by the normal gastric juice in a test-tube experiment, but this result is due to the hydrochloric acid and not to the pepsin. Under actual conditions in the living stomach there is little likelihood that all the bacilli are killed because of the varying acid strength and their mixture with food. Many investigators agree in the conclusion that bacilli, introduced into the stomach with food, sojourn too short a time to be killed.

Light and Other Radiations.—The effect of light is distinctly injurious to the tubercle bacillus. Koch's first observations indicated that cultures were sterilized in a few minutes' exposure to strong sunlight when in thin layers. Diffused daylight required from five to seven days. Here, again, the natural conditions under which tuberculous material may be exposed to light play a very important part in determining the degree of its disinfectant power. The experimental observations give very wide ranges as to the time required to kill tubercle bacilli in sputum exposed to the sun under varying conditions. For example, Migneco, in Italy, found sputum virulent after ten to fifteen hours' sunning, but not after twenty to twenty-four hours during the hottest hours. Mitchell and Crouch, in Denver, Col., found that sputum deposited in sand remained virulent from ten to thirty hours. Delepine and Ransom used a variety of tests with dried sputum, and in the form of dust, which showed a loss of vitality after one to eighteen hours' exposure. Jousset and also Twichell exposed sputum from one to seven hours and found it occasionally innocuous. These results taken together show that a speedy death of sputum bacilli occurs when it is exposed in a dry and dusty condition to sunlight or even diffused daylight. Experiments by Bang, in the Finsen Light Institute, with unconcentrated electric (arc) light acting on cultures, usually killed the bacilli in from three to nine minutes' exposure. The Röntgen rays have been found to be bactericidal to some extent for the cultures of the tubercle bacillus by Rieder, who excluded light and heat rays in his experiments. De Renzi, however, did not discover any effect on sputum. Radium has probably a harmful effect on tubercle bacilli as on other bacteria.

Antiseptics, etc.—The tubercle bacillus is more resistant to chemical disinfectants than most pathogenic bacteria, except anthrax and a few other spore-bearing forms. It is, however, restrained from growth in cultures very readily even by volatile agents, such as hydrofluoric acid (Villemin and Trudeau), formaldehyde, creosote, oil of eucalyptus, peppermint, etc. The commonly used disinfectants, phenol, mercuric chloride, and formalin, require a long time to disinfect moist sputum by reason of its ability to resist penetration on account of the coagulation produced on the outer surface which protects the inner portion. Five per cent. phenol is slow in action, requiring twenty-four hours in Schill and Fischer's tests upon sputum, while even 2 per cent. mercuric chloride was not effective. Since the practical usefulness of disinfectants must depend upon the penetrative power, those which have a solvent action are to be preferred. In this class is lysol, which is effective in 1 per cent. solution. Other combinations of soap and the kresols are very valuable. Two per cent. lysol is the most useful agent to disinfect sputum in cuspidors, but its odor is prominent; caustic alkalies and strongly alkaline soaps suffice to render sputum harmless in suitable receptacles. Calcium hypochlorite is an excellent disinfectant for sputum and feces. The use of formaldehyde gas has practically displaced sulphur for the fumigation of rooms, and the results are satisfactory in disinfecting the surface of objects exposed for a sufficient time to the moist vapor in a well-sealed room; this is not always accomplished, and bedding, rugs, and objects likely to have folds, if contaminated with smears of sputum, escape disinfection. Masses of sputum large enough to be visible cannot be rendered harmless by ordinary fumigation.

Chemical Composition.—Nucleoproteins or Nuclein.—Mucin-like substances were extracted from the bacilli by Weyl and Hoffman and identified by Kühne and de Schweinitz as nucleoproteids. Later, Ruppel and Levene independently examined the reactions and analyzed the decomposition products of this ingredient, which proved to contain the essential poison. This is a peculiar nucleic acid present in the body of the bacillus and its soluble secretions. The cement-like substance which agglutinates the bacilli in masses is composed of this nucleoprotein. Digestion of the bacilli with pepsin or trypsin removes but little substance, and saline extracts also contain very little simple protein. Levene discovered three forms of nucleoprotein in bacilli grown on synthetic media. They differed in solubility, heat coagulation point, and phosphorus content. The so-called toxins formed in the broth cultures are identical with these, and appear to be dissolved out of the bacilli rather than secreted from them.

Nucleic Acid or Tuberculinic Acid.—The decomposition of the nucleoprotein above described sets free a special nucleic acid containing from 9 to 11 per cent. of phosphorus. It can be precipitated by alcohol and forms the most toxic substance yet isolated from the tubercle bacillus. By further decomposition tuberculinic acid is split into thymin and a neutral substance called "tuberculosin" (Ruppel), besides several bases. Levene and Kitajima also found thymin in the nucleic acid. The effects of tuberculin were ascribed by v. Behring to the thymin

fraction in the nucleic acid. In the precipitated nucleoprotein is found "tuberculosamin" (Ruppel), a protamin which is a base in combination with the nucleic acid. The most striking peculiarity of this toxic nuclein is its extraordinary resistance to heat and chemical decomposition.

Fats and Wax.—Second only in importance to the nuclein are the fats. Estimates of the proportion of fat in the bacilli vary from 10 to 40 per cent., far in excess of all other bacteria; and the quantity depends on the age, rapidity of growth, virulence, and composition of culture medium. The alcohol and acid resistance is ascribed to an as yet unidentified alcohol by Bullock and McLeod, by others to a fatty acid.

Secretions during Growth.—There is no evidence that tubercle bacilli secrete or excrete anything in cultures during active growth except a trace of volatile fatty acid and a slight amount of soluble nucleoprotein having the same reactions and properties as that obtained by maceration or extraction of the bacilli. It is probably set free from degenerated or dead bacilli. The fatty acid is the source of the almond-like odor developed in cultures. Differences between the acidity of human and bovine broth-culture filtrates have been noted by Theobald Smith, which he regards as a means of identification. The human broth cultures acquire an increased acidity, while the bovine become more alkaline. The significance of this has not been determined definitely, although the higher percentage of free fatty acids found by de Schweinitz and Dorset in human bacilli is suggestive, since the presence of glycerin was found to bear some relation to the production of the acid reaction.

Tuberculin.—This term was applied at first by Koch to the filtered and concentrated broth in which full-grown cultures had been boiled. It contained, therefore, a glycerin-broth extract of the bacilli, together with such soluble products of the bacilli as were formed during their growth and not precipitated or destroyed by heat. This original tuberculin, or "T. O." (also called "old tuberculin," "A. T."), was the first of several modifications experimented with by Koch. The tuberculin in which Koch last interested himself is known as "A. F." ("albumose free"), being prepared from cultures containing no peptone.[1]

Analyses by Ruppel identified the active substances in tuberculin with the nuclein and tuberculinic acid previously described. It is precipitated by 66 per cent. alcohol and the re-solution of this precipitate was called "purified tuberculin." Tuberculin in this form when subjected to tryptic ingestion wholly loses its activity, thus indicating its essential combination with protein. It is, however, very resistant to physical and chemical agencies, heat, light, etc., and loses but little activity in concentrated form by age.

Modifications.—A great variety of tuberculin modifications have been prepared, most of which aimed to eliminate reacting substances while preserving the curative element. Others are intended to rid it of extraneous matter or to avoid heat in its preparation. Since it is now known that the reacting substance, the protein (or "antigen"), is the only important thing in tuberculin, all efforts to purify it simply

[1] Jochman u. Möllers: Veroff. d. Koch-Stiftung., 1912, vol. iii.

weaken its activity. For therapeutic purposes there are theoretical advantages in favor of pure solutions of the nucleoprotein, yet the crude preparations serve equally well in practice. There is also no perceptible difference between the tuberculins made from human and bovine bacilli. Quantitatively considerable differences are observed which have been erroneously interpreted as fundamental.

Vaccines.—The tuberculins are also prepared from pulverized and emulsified bacilli, either unchanged or extracted with water and other solvents. Since the active substance in these is combined with the waxy ingredients of the bacilli they are slower of absorption but all produce characteristic reactions.

While different new tuberculins have multiplied they are all comprised in the two classes above described—namely, extracts and emulsions.

Tuberculin R ("T. R.") (Koch) was introduced in 1897 as an improved form of tuberculin for immunizing as well as therapeutic use. In contrast to the various extracts it is an emulsion of the residue from living, virulent bacilli after pulverization and extraction with water and suspension in 20 per cent. glycerin.

"Bacillen Emulsion" ("B. E."), Koch's later product, consists of an emulsion of the entire substance of the pulverized living bacilli in 20 per cent. glycerin, only the coarser particles being excluded. Glycerin is depended upon to sterilize any bacilli not removed by centrifugalization. The emulsions are slower of absorption and for therapeutic use require longer intervals between doses.

To aid absorption F. Meyer[1] prepared "sensitized" bacillus emulsions ("S. B. E.") which were treated with an immunized serum to absorb the immune body and thus help the tissues to take up the emulsified bacilli after injection.

"Bovovaccine" (v. Behring) was the first immunizing virus introduced by v. Behring for cattle, and consists of unsterilized dried bacilli from a human culture passed through guinea-pigs. It is used intravenously and keeps but one month.

"Tauraman" (Koch and Schutz) was the analogous vaccine for cattle introduced by Koch, but is preserved in a more virulent condition. It is used intravenously.

"Bovovaccine" (Klimmer[2]) purports to be a human strain of tubercle bacilli made avirulent by passage through salamanders.

Living bacilli of weakened virulence or completely avirulent have been employed for humans therapeutically and for immunization by several experimenters (F. Klemperer,[3] G. B. Webb,[4] Friedmann[5]). The matter has experimental support, but is yet on trial.

It may be said of the various tuberculins that, viewed from a chemical standpoint, they all contain the peculiar nuclein substance or its derivatives in greater or less quantity and degree of solubility. In some the

[1] *Berl. klin. Woch.*, 1909, p. 2265.
[2] *Zeitschr. f. Tuberkulose*, 1908, xii, 352.
[3] *Zeitschr. f. klin. med.*, 1905, lvi, 241.
[4] *Jour. Med. Research*, 1909, xx, 1.
[5] *Berl. klin. Woch.*, 1912, xlix, 2214.

endotoxin has been altered or decomposed by heat or extractives, but all are capable of producing the characteristic reaction in tuberculous subjects. The vaccines form either preparations of living bacilli or their substance as nearly unchanged as possible.

Chemical Pathology.—*Action of Dead Bacilli.*—It was early demonstrated that dead bacilli could produce tubercles essentially identical with those caused by living bacilli. Caseation is, however, absent unless large amounts are injected, which generally lead to abscess formation in subcutaneous injections. Besides the local effects, Maffucci and his pupils showed that nephritis, atrophy, and disturbance of nutrition such as are seen in the cachexia of advanced tuberculosis can be produced by sterilized bacilli. Koch, in the experiments upon tuberculous guinea-pigs which led to the discovery of tuberculin, found that dead bacilli injections modified the course of the disease so as to cause healing of the inoculation ulcer; many others confirmed and extended these observations.

Effect of the Nuclein.—As already mentioned, nearly all the extracts obtained from tubercle bacilli contain the poisonous nuclein or its decomposition products. The effect of moderate doses on healthy animals of the water or glycerin extracts is not immediately harmful. Repeated large doses produce fever and wasting without noticeable microscopic changes. Large doses cause death in healthy guinea-pigs in twelve to forty-eight hours from slow collapse, the only microscopic lesions being local extravasations at the site of injection. In tuberculous animals very small doses cause high temperature and local reactions at the seat of disease, accompanied by a polynuclear leukocytosis. Very moderate doses cause death in a few hours, with hypothermia, leukopenia, and extensive extravasations of blood about the tubercles.

Intravenous or intrameningeal injections produce all the symptoms of acute anaphylaxis which is also shown by non-tuberculous animals previously injected with the same extract (Baldwin, Krause[1]).

Von Behring and Ruppel prepared pure tuberculinic acid whose toxicity was very great for tuberculous guinea-pigs, but further decomposition of this toxin weakened its effect. De Giaxa also produced coagulation necrosis with the nucleic acid prepared from tubercle bacilli. In its most insoluble form the nuclein probably gives rise to the so-called "tuberculin hypersusceptibility," because of its very slow absorption and the specific adaptation required of the cells to absorb and disintegrate it.

Effect of the Wax.—When isolated in a pure form, the alcohol, ether, chloroform, or benzole extract has the effect upon the tissues of an insoluble irritant. Auclair has produced caseation by means of the ether, chloroform, and xylol extracts, and ascribes to the fatty secretions of the bacilli the caseating property of the tubercle bacillus. It is undoubtedly true that the fatty acids in tubercle bacilli play some part in the coagulation necrosis of tubercle, but it is very doubtful if they are the chief agents.

[1] *Studies from Saranac Laboratory*, 1904–1910.

Volatile distilled products of tubercle bacilli have not been isolated in quantities sufficient to establish their probable importance in the disease. The local effects of tubercle bacilli may fairly be attributed to the highly resistant wax, combined with the necrotizing action of the nucleic acid and fatty acids. It is uncertain whether these caseating substances are chiefly set free during the multiplication of the bacilli or after their death and disintegration. The soluble products of the bacilli which have thus perished are unquestionably the cause of the constitutional symptoms in tuberculosis, such as the fever and anemia. Moreover, the toxemia closely resembles that produced experimentally by the nuclein or dead bacilli above described. Maragliano claims to have found a toxin in the blood and urine of cachectic consumptives which produced tuberculin effects, while others have demonstrated albumoses in the urine (Lenoir) and sputum (Simon) which resembled tuberculin.

Effect of Tuberculin.—The phenomena of tuberculin poisoning have already been described as those of the endotoxin or nucleoprotein of the tubercle bacillus. The chief interest centres about the local reaction in tuberculous foci and in the acquisition of tolerance or immunity to this poison by all the tissues. In moderate doses no perceptible effect is produced upon the tissues or blood in health. Large repeated injections into the veins have caused endarteritis, degeneration of liver and kidney epithelium, followed by atrophy of these viscera or sudden anaphylactic spasm. All forms of tuberculin act similarly in causing local reactions about tubercles, but vary greatly in the time and intensity of the reaction, owing to their greater or less solubility. The original tuberculin acts more violently than some of the modifications, doubtless because it contains more of the simple derivatives split off by heat from the macerated bacilli.[1]

Local Reaction.—The marked local selective action upon the tubercles which characterizes tuberculin requires detailed description, for it illustrates the mechanism by which the tissues combat the disease. Following the administration of tuberculin, within four to twelve hours dilatation of the small arterioles and capillaries surrounding the tubercles takes place, and a serous and cellular exudate follows sufficient to cause visible swelling in the case of lupus; the zone of lymphoid and epithelioid cells already about the foci becomes augmented by additional cells, chiefly polynuclear leukocytes, and in violent reactions extravasations of red cells may appear. These phenomena reach their height in from six to twenty-four hours and quickly subside, unless very large or quickly repeated doses are given. After forty-eight hours lupus foci have become smaller and less conspicuous than before; and when favorably treated the lymphoid cells are either gradually absorbed or transformed into fibrous tissue as in the natural cicatrization of tubercles undergoing healing. The local reaction varies in intensity according

[1] It furthermore contains the constituents of the broth-culture medium, peptone, and beef extractives, unused by the bacilli in growth. These have some enhancing influence upon the reaction in large doses, but for the purposes of diagnosis, where it might cause confusion, this is inappreciable.

to the situation, extent, and age of the tubercles, as well as the sensitiveness of the cells composing the tubercles in responding to the toxin.

Neither the local nor general reaction is absolutely specific; various nucleoproteids, yeast nuclein, bacterial proteids in general, and digestive products, such as albumoses, are capable of producing similar effects. Cinnamic acid, cantharidin, pilocarpine, and other alkaloids also act to some degree, although less as local irritants than general leukocyte stimulants. There are analogies in other diseases with focal points of infection, such as anthrax, syphilis, and streptococcal infections, in which local and general reactions may result from a specific stimulus. Moreover, tuberculous subjects are well known to be markedly sensitive to fever from transient mental or physical excitement as well as digestive disturbances. A slight increase in the lymph flow from the heightened blood pressure can cause more absorption from the foci. These facts have tended to discredit the value of tuberculin as a delicate diagnostic agent, but in practice need not cause confusion in cases of recent tuberculosis.

Theories of the Reaction.—The explanation of the reactive phenomena has been puzzling, and several contradictory theories have been proposed which need not be reviewed. The most satisfactory theory, which accords with modern immunity studies, is in essence that first proposed by Eber, Bâbes, and Proca, and modified by Theobald Smith, which assumes an enzyme activity in the cells immediately surrounding the bacilli and their products. Under ordinary conditions a slow disintegration and digestion of the bacilli takes place, but with the added stimulus of tuberculin injections the process is accelerated in the foci; if enough irritation has occurred, soluble or partly digested products of the bacilli are freed which are sufficient to cause local and general reactions.[1]

Repetition of the injections in increasing doses gradually creates a tolerance which is explained in these ways: (*a*) by the fixation of the tuberculin by antibodies before it reaches the tubercle, probably by precipitins; (*b*) by its rapid digestion and transformation into harmless products by lysins and the exhaustion of tuberculin in the tubercle accessible to the reacting cells. The tolerance is not a lasting one, as the reaction power may return after cessation of the injections so long as cells remain which retain sensitiveness.

The Mechanism of Resistance and Immunity.—The animal tissues present a certain degree of normal resistance against the invasion of the tubercle bacillus. It is obvious that the normal resistance may become gradually increased by many exposures which have been successfully overcome without the development of actual disease; this general

[1] The recent additions to our knowledge of the nature of hypersensitiveness to foreign proteins introduced into an animal outside the normal digestive tract have provided the best proof of this. Tuberculin sensitiveness is tuberculoprotein anaphylaxis. It is thought by Wolff-Eisner, Friedberger, Roemer, and Joseph to be a special form of anaphylaxis, but Baldwin and Krause found that anaphylactic reactions identical with those of other proteins can be produced with tuberculonucleoprotein, employed either in a pure form or as crude tuberculin. The reactions in the focus are to be regarded as peculiar only because the cells are more highly specialized than elsewhere to digest the foreign protein, *i. e.*, tuberculin.

biological law finds no exception in the case of tuberculosis, although in case the infection has once taken root in an individual, even if recovery takes place, a subsequent increased susceptibility to tuberculin appears.

The protecting mechanism is feeble in infancy, but if early infection is avoided or successfully prevented without a foothold gained by the bacilli, the adult human individual in normal health seems to be practically immune to natural infection. From the present aspect of the problem of infection, we must conclude that the mucous membranes and lymphatic tissues are chiefly concerned in the primary resistance, rather than the pulmonary alveoli, as formerly supposed.

The tubercle forms the object of study as the unit or type of the mechanism of resistance; for the tissues in general experience but slight effect from the presence of a few tubercle bacilli well localized, and there results a lack of effective resistance from absence of a general stimulus at favorable moments in most cases of chronic tuberculosis. The ultimate result consequently often depends on the efficiency of the cell nutrition throughout the body to bear repeated severe exposures to infection without harm.

Heightened Susceptibility to Auto-infection and Tuberculin. — This characteristic is one of the results of a previous infection and may arise from partially healed or latent tubercles as well as recent active disease. Koch first noted that a second infection produced marked reaction at the point of inoculation without spread of the infection from this point, and it led to his discovery of tuberculin. Von Baumgarten also studied the phenomena of primary and secondary infection. More recently Roemer[1] and Hamburger[2] have repeated these experiments to show the immunity conferred by the first infection. Straus and Gamaleia observed that great sensitiveness had been acquired by animals injected with dead bacilli to a repetition of the injections.

The analogous results with tuberculin are well known, severe, and even fatal reactions being possible in tuberculous subjects from doses which are practically inert for healthy persons. The subject has been thoroughly studied by v. Behring, Theobald Smith, Trudeau, and others, and the conclusion is unquestionable that the phenomenon is one of specific resistance. There are analogous hypersensitive reactions resulting from the injection of various foreign serums and other proteins, the so-called "serum disease," whose symptoms and period of development are closely comparable and leave no doubt of a close relationship. Von Behring finds in *natural* infection of calves that three months is the usual period required for tuberculin susceptibility to develop to a noticeable degree. It requires from eight to fourteen days after experimental inoculation in guinea-pigs (Trudeau[3]). From this time fever and local reactions follow the injection of tuberculin. This period is the same which is required for the formation of all kinds of antibodies, and we may infer that the development of reaction susceptibility signifies a lytic power or an affinity acquired by the cells of the tubercle

[1] P. Roemer and Joseph: *Beit. z. Klinik d. Tuberk.*, 1910, xv, 31; 1911, xvii.
[2] Hamburger and Toyofuku: *Ibid.*, 1911, xviii, 163.
[3] *Studies from Saranac Laboratory*, 1900–1904.

acting both on its own accumulated toxin and the injected tuberculin, which liberates a poisonous substance or "anaphylatoxin" affecting the whole organism.[1] This susceptibility has an important bearing both on the development of new foci in the presence of existing disease, and the acquirement of immunity of which it is probably a necessary accompaniment.

So long as this susceptibility persists, there is reason to expect that new infections with tubercle bacilli will be localized at the point of entrance into the tissues, and that they are either disposed of there without actual infection or produce foci with ulceration, as in the larynx and intestine during the later stages of pulmonary tuberculosis or during periods of lowered resistance.

This reaction power implies a certain change in the organism in reference to the tubercle bacillus which causes an immediate response by the tissues. The reason why this condition does not mean efficient immunity in all cases is explained by Theobald Smith as due to the greater vulnerability of the lungs, in which a second auto-infection is prone to occur and be focussed, instead of being carried into the lymph nodes and destroyed as in a primary infection. An external exposed focus in the more vulnerable lung tissue is thus to be regarded as more dangerous for the individual whose specific immunity is not developed than for one who has only normal resistance, and where the number of bacilli is infinitely less than from ulcerating tubercles in the diseased person. On the other hand, this very sensitiveness probably acts efficiently in preventing further infection from outside. Von Behring, from his investigations in cattle tuberculosis, regards this sensitiveness in the light of an actual acquired predisposition, and believes that it can persist for some time in cattle after an inoculation of human bacilli, even when no tubercles can be found. He is inclined, nevertheless, to doubt that this predisposition favors a renewed infection from without; rather does it oppose this, but promotes its further spread in the individual with *already latent* disease. In the present state of our knowledge this reaction susceptibility cannot be considered a necessarily unfavorable factor in an adult individual who has a clinically healed pulmonary tuberculosis. In fact, the experiments of Roemer and Hamburger indicate that reinfection means auto-reinfection and not the acquisition of bacilli from an external source.

Immunity.—No disease has shown so little apparent evidence of immunity acquired by one attack as tuberculosis. The universal clinical experience seems to oppose such a possibility. Nevertheless, there are certain characteristics of the clinical course of the disease, and in some cases of recovery, which on closer examination point to an acquired resistance which amounts to practical immunity. Even the more chronic course of the disease, seen, as a rule, in persons classed formerly as "hereditarily disposed" and scrofulous, but now regarded as instances of early infection, may be regarded as a sign of specific resistance.

[1] The delicacy with which the reaction occurs in response to minute doses of tuberculin in the incipient stages of tuberculosis is often increased by repetition of the same dose within short intervals. This fact forms the basis of a method of tuberculin diagnosis advocated by Loewenstein and Rappaport.

Likewise, the slow progress and often benign course of tuberculosis in subjects beyond middle age are readily attributable to an acquired resistance due to previous infections.[1] Both Turban and Solly found a greater percentage of chronic, prolonged, arrested cases among those patients with family tuberculosis who do not die in the onset of the disease than those without such a history. Unfortunately, such comparatively mild infections as are seen in persons with weak constitutions of phthisical build are not often really recovered from in the sense of restoration to robust health; the disease no longer progresses, but secondary anemia, weak digestive function, and poor assimilation frequently accompany an actual disappearance of the former symptoms. H. M. King has made the interesting observation that the course of the disease in 103 fatal cases was a year longer in subjects of phthisical parentage than in those without it. Such facts speak quite as much for acquired resistance from repeated early infections as for inherited immunity. Nevertheless, the acquisition of relative immunity by certain families and races which have long been subjected to the conditions of life favorable to tuberculosis and exposed to the infection, has considerable support in connection with the Jewish and English races, who have intermarried less with other races than those of Central Europe. Reibmayr holds this theory and predicts a diminution and decreasing virulence of tuberculosis comparable to that of syphilis. Roemer[2] points to the acquired immunity of long infected races in contrast to the acute forms of the disease in peoples less exposed.

Experiments in Tuberculosis Immunity.—The first encouraging results from experimental researches on tuberculosis immunity and specific treatment began with Koch in Germany, Hericourt and Richet in France, and Trudeau in America in 1889–90. A host of others have followed with notable contributions, among whom de Schweinitz, MacFadyen, Maragliano, Pearson and Gilliland, Koch and Neufeld, Valleé, Theobald Smith, Baumgarten, should receive special mention. Von Behring and his associates, especially Roemer, have unquestionably made the most extensive investigations, and practical results were apparent in his "bovovaccine" method of immunizing cattle with human bacilli, and the coincident application of the same principle by the American veterinarian, Pearson.

The very persistent studies and animal experiments in this field have at least demonstrated that a high degree of artificial protection is possible against tuberculosis. Complete immunity under extreme conditions of experimental inoculation has proved disappointing as compared with some other diseases. The duration of the immunity under the most favorable methods in calves has not exceeded two years from a single protective inoculation. By repetition of the inoculation the specific immunity can be extended, but the uncertainty as to the fate of the living human bacilli used for the protection renders the method imprac-

[1] The exacerbations during the course of the disease often have a well-defined limit, ranging from ten to fifteen days, which is significant when taken in connection with the period of antibody formation in the blood after bacterial inoculations.

[2] *Beitr. z. Klinik d. Tuberk.*, 1912, xxii, 301.

ticable for dairy cattle at present. The same reason obviously forbids its employment in young infants, since it has been found that living bacilli from the vaccine may remain latent for many months in calves. It has not been shown that, experimentally, bacilli from cold-blooded animals or other acid-fast forms protect better than dead bacilli (Klimmer, Friedmann). The prospects for a passive or transferred immunity by means of serum, milk, or otherwise are not promising.

The production of immunity by means of serum or by extracts of the bacillus has thus far failed of adequate proof and preparations of the living bacillus have provided the best protective vaccine for animal experiments. Some increase of resistance can be obtained by the injection of the various tuberculins and dead bacilli, and it is to be hoped that still better results may be possible along this line without the necessity for the use of living organisms. An ideal vaccine should theoretically contain all the immunizing properties of the living bacteria in a form both incapable of infection and easily absorbed by the tissues. The way seems clear to employ bacilli for immunizing infants provided the bacillus used is avirulent for guinea-pigs and monkeys.

Preliminary experiments have been made by Webb and Williams[1] and Friedmann,[2] the results of which will be watched with anxiety as well as interest.

The Mechanism of Specific Immunity. — Specific immunity against tuberculosis, in the meaning at present understood of immunity to bacterial disease in general, requires an ability on the part of the tissues to disintegrate the bacillus and destroy or neutralize its toxin; in short, a combined bacteriolytic and antitoxic immunity. The question as to the production of a literal antitoxic property is yet a matter of conjecture, for when bacteriolytic power is developed to a high degree, there may still be a lack of complete tolerance of the toxin. It is, hence, possible that the disease may be arrested for a time, only to result in a chronic poisoning because of the bacilli disposed of in greater numbers, and whose toxic products the tissues have inadequate power to dispose of at the time most needed. There follows in consequence permanent injury to the cells.

Owing to the restricted action of the bacillus in the tubercle, the cells not composing the tubercle fail to get the proper stimulus to resist its action when the constitutional condition is in a favorable state for this. It is also fairly established that such immunity as is acquired by an animal to this disease rests in its cells and is not discoverable in its serum. This fact forms the chief *rationale* for specific therapy in tuberculosis by tuberculins, for it is desirable to impress the whole organism with a specific stimulus in sufficient quantities and at proper intervals to maintain a high resistance. The exact mechanism of the acquisition of increased tolerance by the cells is undoubtedly a very subtle thing and closely connected with the tuberculin susceptibility phenomena. The evidence is strong that whatever specific immunity may be acquired

[1] *Jour. Med. Research*, 1909, xx, 1.
[2] *Berl. klin. Woch.*, 1912, xlix, 2214.

rests on the function of tuberculin reactivity. It is therefore clear that the methods which have furnished the best degree of protection have produced this reactive condition; in brief, the condition closely resembling if not identical with a tuberculous infection which does not progress.

It is assumed by von Behring that the lymphatic tissues and leukocytes are especially concerned in maintaining immunity. However this may be, the excessive inflammatory reaction seen in experimental inoculation of immunized animals is accompanied by a large collection of mononuclear and polynuclear leukocytes about the bacilli, and all the phenomena of a prolonged tuberculin reaction. Since complete absorption of the focus and disappearance of the bacilli may follow without caseation resulting, it is natural to suppose that the process is an immunity reaction, even though it be only an exaggeration of the normal one which results in caseous tubercles in the unvaccinated animals. In calves immunized by von Behring, tuberculin-reaction susceptibility was lessened before he regarded them as sufficiently protected, but the ultimate loss of susceptibility was accompanied by loss of immunity. The best conception, therefore, of the mechanism of immunity against tuberculosis is that of a heightened digestive power of the body cells for tubercle bacilli, *i. e.*, tuberculin reactivity.

Antibodies.—Agglutinins or precipitins are readily produced against tubercle bacilli and their products by repeated injections of these substances, and appear to some extent in the course of the disease, as found by Arloing and Courmont and others. A high agglutination power nevertheless may exist without immunity, as in the course of typhoid fever. A close relationship obtains between the precipitins and agglutinins of tubercle bacilli as they are interacting upon the solutions and emulsions of the bacillus substance, and they are doubtless identical substances.

Opsonins which aid in the phagocytosis of tubercle bacilli have been distinguished as specific antibodies quite distinct from the agglutinins by Wright and Bullock, and have some similarity to the serum complement. This function prepares the bacilli for ingestion by the leukocytes and can be increased by tuberculin injections. It may therefore have some bearing on the production of immunity, but its relative importance is undetermined. Neither can the opsonic index alone nor the agglutination test at present be regarded as a measure of immunity nor of absolute diagnostic value for tuberculosis, because normal agglutinins and opsonins which act on tubercle bacilli to a greater or less degree are present in healthy persons.

"*Antitoxins*" or *antituberculins* have been demonstrated by Maragliano and others in the serum of animals injected with extracts of bacilli. Their true nature is in doubt, and although they have been claimed to neutralize fatal doses of tuberculin, it is not clearly established that they are analogous in action to those of diphtheria and tetanus, whose toxins are of a different nature. The presence of a bacteriolysin has indeed been claimed for Maragliano's serum.

The antituberculosis serum of Ruppel has been used successfully in preparing anaphylactic poison from tubercle bacilli, and it is doubtful

that any true neutralizing antibody is contained in any serum in the sense of an antitoxin. Pickert[1] claims this for antituberculin sera.

Bacteriolysin.—It has been difficult experimentally to demonstrate a bacteriolytic power in serums acting on tubercle bacilli *in vitro,* probably owing to the inherently great resistance of this organism to disintegration and the long time required for such action. Moreover, the participation of living cells may be an essential condition not susceptible of imitation in the test-tube. The existence of such a function is, nevertheless, undoubted, as progressive stages of disintegration in the bacilli introduced into immunized animals are manifest by staining.

Amboceptors for tubercle bacilli and tuberculin are readily demonstrated by the usual methods of complement deviation. They are possibly identical with the specific agglutinins and lysins. Much and Loescke[2] also find amboceptors to the fat of tubercle bacilli.

The therapeutic experiments with tuberculosis serums have usually been disappointing or unconvincing as to a specific value. Some have proved harmful, like those of Maffucci, Bâbes, and v. Behring. Furthermore, too little attention has been given to the physiological effect of repeated injections of heterologous serums apart from any specific antibodies that they may contain.[3] Therefore, the outlook for a successful serum therapy in tuberculosis cannot be regarded as hopeful at present.

To summarize the present knowledge of specific reaction products against tuberculosis, we can say that specific agglutinins and opsonins are readily recognizable in the serum and that probably lysins or digesting functions exist which act in conjunction with the body cells to produce relative immunity.

Conditions Influencing Infection.—Number and Virulence of Tubercle Bacilli.—On the part of the tubercle bacillus the dose and virulence must be conceived to be of prime importance. It has been shown in animal experiments that a moderate infection may be completely overcome while a greater one is fatal. It is thus intelligible that repeated and frequent exposures seem ordinarily necessary to produce the disease in human adults. If a single exposure were sufficient, the fact would be difficult to prove anyway, because of the slow development of the disease; yet its occurrence cannot be considered impossible, especially in children. The actual number of bacilli in room dust capable of floating in the air is small compared with those in the heavier particles of moist or dry sputum on the floor or contaminated clothing which cannot remain suspended. Hence, the number of bacilli swallowed must be much greater than those inhaled however they are taken in, and a single exposure might be sufficient to infect a child in this way.

The virulence is also known to be variable. Some strains of tubercle bacilli are able to infect in the minutest dose when implanted in susceptible animals, while others seem very feeble. Clinically this fact may be only surmised by the different forms of the disease, whether chronic

[1] *Deutsch. med. Woch.,* 1909, xxxv, 1514.
[2] *Beit. z. Klinik. d Tuberk.,* 1911, Band xx.
[3] Normal serums alone under these conditions have been shown to excite antibodies against the serum *per se,* whose effects must be reckoned with.

or acute, and by instances of apparently direct contagion, where the disease develops in rapid succession in a number of unrelated individuals. What the virulence of a given strain may be is difficult to determine from the course of the disease in human subjects, where so many other factors enter into the problem.

Natural Resistance.—In analyzing the nature and mechanism of man's natural resistance to tuberculosis, one must include his environment relative to climate and altitude; his residence, whether urban or country, together with his occupation and cellular defences. The greater purity of the air and less strenuous life of the country dweller naturally contribute to the maintenance of normal vigor.

In the first rank for the natural protection of the individual is the epithelial covering of all surfaces exposed to external influences. The external skin is not easily penetrated by tubercle bacilli unless a lesion exists, and it offers an effective barrier in adult life, though less in childhood. The nasal and pharyngeal mucosa with intact ciliated epithelium is a strong defence, as is also that of the trachea and bronchi; the normal adult gastro-intestinal tract likewise appears but slightly permeable. If the infection gains entrance, there are other mechanisms set in operation which tend to fix the bacilli at the portal of entry or to check its progress in the neighboring lymph nodes. These are comprehended under the head of immunity reactions, elsewhere considered.

At present the sum of our knowledge of good physiological resistance is expressed indefinitely as good cell nutrition. Hence, good eaters with sound digestions are well armed against this disease. The "gouty diathesis" is undoubtedly an evidence of relatively greater resistance to tuberculosis according to clinical experience, while certain diseases mechanically oppose it. Mitral valve disease with resulting pulmonary venous stasis acts as a protection possibly for that reason, yet the matter is rather too complicated for positive proof. Emphysema is also supposed to afford some degree of immunity against tuberculosis. An open-air occupation or one requiring active muscular exercise is another important aid to resistance. Musicians who play wind instruments are infrequently tuberculous, according to Rogers. Certain occupations have been claimed to be especially protective against tuberculosis because of the gases inhaled by the workmen. The proof of such a protection is not convincing enough for serious attention. Agricultural pursuits and a seafaring life are naturally best adapted to maintain a strong constitution if other conditions are favorable. Lastly, a naturally vigorous mental and moral equipment is second only to the physical.

Reduction of Resistance.—*Disposition.*—A well-founded belief in a "tendency" to tuberculosis has existed in all ages. It received a check at the time of the discovery of the bacillus, and is still belittled by the contagionists (Cornet). A broader view has again taken root which modern biological research supports, and which claims the acceptance of a middle ground, giving due prominence to both the parasite and host in disease production.

The Nature of Disposition.—A satisfactory definition of the actual nature of what we term disposition or predisposition is as yet wanting.

In the last analysis it has to do with the cell activities of the animal body. It may include a positive element in that the soil is abnormally favorable by reason of a certain chemical composition or functional excess of the tissue metabolism, or, on the other hand, a negative one which consists in the absence of some chemical ingredient or weakness of the normal defensive mechanisms. On the surface, the chemical theory of predisposition has support in the well-known susceptibility of diabetics, because sugar is known to be a favorable component of culture media for the tubercle bacillus. The grade of alkalescence of the blood and especially of the bronchial mucus has also been suggested as a factor (Hesse), since an alkaline sputum is a more favorable culture medium. There are other theories, such as variations in the composition and structure of the elastic fibers (Hesse, Tendeloo); in the amount of silicates in the connective tissue (Kobert, Schulz); the "demineralization theory" of the French authors (Robin and Binet), which assumes a deficiency in the tissues of mineral salts, especially of calcium and the phosphates, due to increased respiratory change or excess of oxidation and the converse of the gouty diathesis, which is accompanied by an excess of these salts. All these theories have found support in the analyses and experiments of their authors, but are too narrow, and lack completeness for a subject of such complexity.[1]

Natural Predisposition.—*Race.*—The question of racial differences in susceptibility has already been noted. It is yet undecided what factor or factors are most important in the apparently greater vulnerability of the Negro and aboriginal Indian races. An attractive theory is that they at present lack the gradual immunity acquired by more resistant races through centuries of civilization and exposure to the infection, the more resistant individuals having survived among the latter. From this point of view racial susceptibility is simply a passive quality rather than a peculiarly different soil.

Heredity.—One of the most complex problems in medicine is that of an inherited disposition to tuberculosis. Theories have changed as new facts have developed, but the belief in such family inheritance is well-nigh universal. Elaborate statistical studies and genealogical tables have been made by Riffel, Leudet, K. Pearson, and others to show the predominant influence of heredity, even to the one-sided view that the infection is of secondary importance; on the other hand, Cornet, v. Behring, and Boeg ascribe little if any importance to heredity. Practically the only question to be decided is whether an inherited weak constitution has a *specific* tendency to implantation of the bacillus. J. E. Squires gives valuable evidence against the importance of specific susceptibility by comparing the children of consumptive parents with those of non-consumptives of the same class and condition in life. He found only 10 per cent. more of the former had become tuberculous in a study of 1000 families, an excess easily accounted for by the greater opportunities for infection rather than actual heredity. Sutherland[2]

[1] A good review of the subject is found in the very complete work of Schlueter, *Die Anlage der Tuberculose*, 1905.

[2] *British Medical Journal*, 1912, ii, 1434.

confirms this in a more recent study aided by the tuberculin test, in which the children of parents with open tuberculosis were found more often infected than those of closed cases. On the other hand, Karl Pearson,[1] in a study of 300 families, considers the inheritance of a tuberculous diathesis clearly proved.

A truly specific inherited susceptibility must imply transmitted properties through the germinal cells, and strictly construed should not include influences acting during intra-uterine life, which are really congenital. Adami believes that two possibilities may result from parental tuberculosis; according as the disease is progressive or unresisted the germinal cells become weakened by the specific poison, and the offspring especially susceptible to tuberculous infection; or if well resisted the child may acquire an increased resistance to the same disease. Some experimental support to this idea has been attempted, but the matter is hard to control.[2] Moreover, the argument of Hueppe, who is an exponent of the importance of disease predisposition, may be adduced, that "immunity and immunization directly prove biologically that predisposition must be a positive property of the protoplasm, for otherwise there could be no immunization."

Certain clinical observations tend to confirm a belief in an inherited specific susceptibility of a certain kind. One of the most interesting and suggestive is that of Turban on the inheritance of a *locus minoris resistentiæ*, whereby the disease was found to begin in the corresponding lung of the parents and the children in 19 families out of 22 (86.4 per cent.). Among the writer's cases, 78 per cent. of 28 families in which parental tuberculosis existed had children with the corresponding lung first involved. In one family the father and four children had the same lung first affected. Ogilvie found similar instances.

The inheritance of nutritional faults and structural defects in the chest, size of heart and arteries, cannot strictly be classed as specific qualities established by the parental disease in all cases, since they may proceed quite certainly from non-tuberculous individuals.

Defects of development or other diseases in the parents often stamp sufficient weakness upon the offspring to constitute a lessened resistance to tuberculosis quite as important as that entailed by tuberculous parents upon theirs. Prominent among these parental diseases is syphilis; alcoholism and various psychoses are also regarded by many as of great importance. It is only in the broadest meaning that the inheritance of predisposition to tuberculosis can be considered of special importance, *i. e.*, any defects or injurious influences acting upon the parent may possibly be a source of predisposition for the child.

Constitution or Habitus Phthisicus.—Constitutional weakness or maldevelopment (whether truly inherited or congenital) has always claimed importance as a disposition to tuberculosis. Hippocrates described

[1] *Draper's Company Research Memoirs*, 1907, vol. ii.

[2] As an evidence for something specific actually transmitted from the maternal side to the young, the experiments of Baldwin and Krause (*Studies from Saranac Laboratory*, 1904–1910) prove the inheritance of tuberculoprotein hypersensitiveness. This, however, is not manifested by the offspring of tuberculous animals untreated by protein.

the *habitus phthisicus* as the blonde, delicate-skinned individual with winged scapulæ and long, flat chest. Besides the delicate, ovoid-featured type of persons with long, thin bones, known as the tuberculous by the older writers, the scrofulous was also recognized, with broad face, thick lips and nose, coarser skin and heavier figure. In consequence of greater enlightenment these constitutional factors have lost some of their import, although many of the so-called stigmata of tuberculosis undoubtedly favor the disease. The difficulty from our present knowledge of the widespread presence of tuberculous infection in childhood is to distinguish between cause and effect. According to Brehmer, voluminous lungs are associated with an abnormally small heart, which therefore failed adequately to nourish them, thus predisposing to the disease. His system of sanatorium treatment, especially the gradual hill-climbing, was based on this theory.

Bony deformities of the nose and jaws which cause mouth-breathing are now properly included among the constitutional defects. The life insurance companies of today doubtless wisely retain the old conceptions of predisposition in their inquiries about the shape and expansion of the chest and the relation of height to weight, although the tall individual with immobile, flat chest, depressed sternum, and sloping shoulders can no longer be considered necessarily a bad risk. The measurements of Brown and Pope of the patients at the Adirondack Cottage Sanitarium tend to deny any special type for the tuberculous chest, although there was some tendency for the thoraces to be slightly rounder, flatter, and of greater length than normal. The favorable types of the disease, however, are selected for this institution. Among 647 patients of a poorer class in the clinic at Cracow, Poland, only 38 per cent. exhibited a phthisical form of chest, 41.6 per cent. with and 36 per cent. without tuberculous heredity (Kwiatkowski). Turban, whose patients belong to well-to-do classes, found 36.3 per cent. with a *habitus phthisicus*. It is evident that many anomalies when combined in the same person may form a constitutional disposition, but singly have little importance, since they may be compensated for without impairment of the general vigor.

Local Predisposition.—A local disposition natural to certain tissues or organs, especially the lung apices, has much interest and possible importance. Most of the theories urged as the cause of primary apical disease can be expressed by the term local malnutrition. The mechanical theory of the older authors, which attributed the local weakness to a lessened aeration and greater opportunity for the retention of dust due to the poorer expulsive power of the apices, has become less tenable since the knowledge that by hematogenous infection as well the apices are primarily involved in man. The stagnation of secretions and poorer aeration are thus a source of lowered resistance to the tissues, whether the infection be aerogenous or hematogenous. An abnormally great predilection for this situation in some individuals, according to Birch-Hirschfeld, is caused by congenital or acquired irregularities, with narrowing of the posterior apical bronchi. The possible relation of Turban's inherited *locus minoris resistentiæ* to this fact is noteworthy.

Freund first called attention fifty years ago to a narrowing of the apices associated with a premature ossification of the first rib cartilage, which restricts the development and causes greater immobility of the apex. Hart,[1] in an exhaustive monograph, has emphasized anew the importance of Freund's theory in local predisposition and the inheritance of this anomaly. He considers that it gives rise to a shortening of the first rib and a "stenosis" of the apex, and is dependent upon deficient development of the first-rib cartilage or the rib itself on one or both sides. Rothschild,[2] furthermore, found the same predisposition connected with insufficient movement at the sternal joint between the corpus and manubrium at Louis' angle, which is favorable to the paralytic type of thorax. Cornet thinks the greater frequency of right apical disease is due to the larger right bronchus receiving more dust.

Taken separately these various anatomical theories do not carry much weight. When, however, they are combined with the physiological conditions of the blood and lymph circulation in the apices as compared with other regions of the lungs, an explanation of the early involvement of the apices becomes clearer. In the first place the atmospheric pressure variations during respiration are much greater in the basal parts of the thorax, as shown by Meltzer and also by Hofbauer, whereas there are almost no variations at the apices. The consequent lesser aeration and rapidity of the blood and lymph flow in the apices favors the lodgement of the tubercle bacilli, while the same reasons render the tissues more vulnerable. The work of Tendeloo[3] led him to a similar view.

Little can be said in explanation of the apparently greater susceptibility of the lungs, kidneys, and joints as compared with the liver, spleen, and muscular tissues. Aufrecht has long maintained that the presence of terminal arteries in the lungs had much to do with the infection, and that the infarcts caused by bacilli in the bloodvessels formed the primary foci. Like conditions may account for localizations in the kidneys and joints.

Age.—The resistance to tuberculosis varies with age and is least in childhood, when the tissues readily permit the infection to enter at various places and be more easily distributed. The lymphatic, meningeal, bone, and joint forms of the disease predominate in early life, but after the tenth year the pulmonary form increases in frequency.

Whether this is due to a greater susceptibility of these tissues in childhood or to a difference in the avenues and opportunities for additional infection is a complex problem. As mentioned elsewhere, v. Behring holds that the pulmonary form in adults is chiefly a sequel to gastro-intestinal or other mucous-membrane infection in infancy, due to the incomplete development and ready permeability of the mucosa, which offers no barrier to absorption. However this may be, there is a tendency in adults for the disease to develop at the site where the infection is presumed to enter in the lungs or mucous surfaces, whereas in

[1] *Die Mechanische Disposition d. Lungenspitzen*, etc., Stuttgart, 1906.
[2] *Der Sternalwinkel* (Angulus Ludovici) in *Anat. Physiol. u. path. Hinsicht*, 1900.
[3] *Ursachen der Lungenkrankheiten*, 1901.

childhood it usually spreads farther before the tissues respond by tubercle formation. Evidence is accumulating that a primary infection is far more frequent in childhood than hitherto suspected, and it is fallacious to consider the frequency of tuberculosis at different life periods as an index of susceptibility at those ages. This depends, as Cornet says, upon external causes and varying exposure to infection.

It has been observed that puberty and the menopause in females are epochs during which the disease may develop rapidly. An apparent inheritance of susceptibility at certain ages is observed in some tuberculous families, whereupon the disease begins in the children as they successively reach the fatal age—usually between eighteen and twenty-five years. These instances are probably associated with infection at an early age, though the facts are used in support of the theory of actual bacillary inheritance.

Sex.—Little difference exists between the sexes in their liability, except that during menstruation, pregnancy, and lactation women are temporarily rendered less resistant. It is even debatable whether pregnancy as such favors susceptibility, but there is no doubt that the strain of labor and the puerperal period gives an impetus to the disease if latent, and increases the danger of infection. In 46 (5.25 per cent.) of the adult females among the author's private patients, pregnancy, labor, or lactation was the predisposing cause assigned. Lupus is nearly twice as frequent in women as in men, according to Cornet's statistics, who also points to the greater incidence of pulmonary tuberculosis in females of tuberculous families as due to greater exposure to infection at home than in males.

Acquired Predisposition.—*Constitutional Diseases.*—*Scrofulosis.*—This much disputed term deserves retention, in the opinion of the writer, only when applied to chronic non-tuberculous enlargements of the lymph nodes, and to constitutional weaknesses of the skin and lymphatic apparatus well described by Virchow, who regarded the condition as due to a maldevelopment of the glands and lymphatics. Repeated microbic infections other than the tubercle bacillus, such as the streptococcus, staphylococcus, and influenza, can undoubtedly cause a persistent hyperplasia of the lymph glands which give a predisposition for tuberculosis. Whether such instances can be distinguished clinically from actual tuberculous lymphadenitis is indeed doubtful. Opinions are not wanting that the entity known as scrofula always indicates tuberculosis. At present the question may still be considered open, while for practical purposes the term scrofulosis can be used to mean an important predisposition to pulmonary tuberculosis, which is associated with it in 25 per cent. of all cases.

Diabetes.—The presence of an excess of sugar in the blood favors bacterial growth, and doubtless diabetics are especially prone to tuberculosis for this reason alone, whether or not other factors are of greater moment. It is estimated that one-fourth to one-half of all diabetics, especially young persons, succumb to tuberculosis in a progressive form.

Syphilis.—This disease may act as a disposing factor in reducing the general vitality, and both diseases are present in many persons of the

depraved class. Turban found a previous history of lues in 6.4 per cent. of 408 cases; Sokolowski in 3 per cent. of 8074 cases; the author, 1.3 per cent. of 1690 private cases. An idea once promulgated that syphilis confers a relative protection against tuberculosis is entirely without foundation.

Psychoses.—An irritable nervous system is so frequently associated with pulmonary tuberculosis that neurasthenia, hysteria, and nervous instability in general have long been considered predisposing factors. Papillon even considers neurasthenia as a symptom of suspected latent tuberculosis. The relation of these characteristics to tuberculosis as effects rather than causes is therefore equally probable. It cannot be denied, however, that those persons who possess by inheritance or otherwise a delicate nervous organization frequently fall victims to the disease. In the true psychoses there is an undoubted predisposition, especially with imbecile melancholics. Snell found that 41.2 per cent. of these and 27.1 per cent. of those with mania died of pulmonary tuberculosis. Epileptic families are also prone to tuberculosis.

It should not be thought that the frequent incidence of tuberculosis is the direct result of nervous disorders, but rather that the defective functions and nutrition of such persons render infection easier. Increased opportunity for infection, especially in public institutions, has possibly played an important part in the past.

Previous Disease of the Lungs and Thorax.—The importance of acute respiratory diseases in developing a latent tuberculosis and favoring a new infection is apparently great. Turban found 34.5 per cent. of his cases preceded by a tendency to inflammations and catarrh of the air passages. The relation of *lobar pneumonia* to tuberculosis is in dispute, some authors holding that the latter is relatively rare as a sequel to pneumonia, and that caseous pneumonia begins as such, while others maintain that it is developed from a latent focus by the pneumonic process. Jacob and Pannwitz found 195 in 3295 cases with a history of precedent pneumonia, and therefore regard it as predisposing. It was found in 110 of the author's 1690 patients in whom a predisposing cause was assumed.

Influenza is a frequent and important agent in bringing latent tuberculoses to light. Allowing for mistakes in diagnosis in which the presence of tuberculosis is overlooked, influenza must be classed as an important exciting cause if not a true predisposition. Jacob and Pannwitz found it to have occurred shortly before the tuberculous outbreak in 479 (14.5 per cent.) of their cases; while 389 (11.8 per cent.) gave a history of antecedent colds. Among the author's cases 262 (15.5 per cent.) gave a history of influenza, and 376 (22.2 per cent.) of colds.

Measles, scarlatina, variola, diphtheria, tonsillitis, and *whooping cough* are in the same category because the lowered resistance produced by these maladies is accompanied by inflammation of mucous membranes and lymph glands in which tubercle bacilli may have already lodged. Von Pirquet[1] found no response to the cutaneous tuberculin test during

[1] *Wien. klin. Woch.*, 1908, xxi, 861.

measles and scarlatina. This condition of "anergy" may well account for the acute outbreaks of tuberculosis when the defensive power is in abeyance. In order to distinguish between the instances of latent infection which are spread by these diseases and those fresh infections for which the soil is made favorable, the time elapsing before the tuberculous outbreak takes place forms some guide. It may be assumed that the longer the interval the greater the probability there is of a new infection having occurred. Measles and whooping cough claim the first rank in this connection. In the author's series of 1690 cases, all aged over fifteen years, the above diseases preceded the tuberculosis in 61 (3.6 per cent.).

Bronchitis Simplex and Chronica.—The frequency of bronchitis and asthmatic affections prior to recognized lung tuberculosis cannot be regarded as causative; rather are they symptomatic of existing tuberculosis. A study of 700 cases of *asthma* by Soca indicated that a large proportion (500) were apparently associated with pulmonary tuberculosis. Asthma was given as a precedent disease in 11, bronchitis in 52 of the author's series. Catarrhal diseases of the upper air passages of a chronic character cannot be considered as *directly* aiding infection except in children, considering their frequency in otherwise healthy persons. On the other hand, nasal obstruction and adenoid hypertrophy are potent aids to infection by causing "mouth-breathers." E. F. Ingalls found nasal diseases in only 28 per cent. of 830 cases of tuberculosis, whereas 75 per cent. of the general population suffer from them. In 29 of the author's cases it was assigned as a factor.

Pleuritis of the primary form is in such a large proportion of instances a symptom of tuberculosis that it needs no further mention here. Secondary pleurisies due to trauma, pneumonia, and other respiratory diseases may act predisposingly.

Rachitis being an expression of defective nutrition favors infection, presumably both for that reason and because of the thoracic deformities which form a *habitus phthisicus* and impair chest movements. It was found in 10.8 per cent. of Turban's cases. Well-marked deformity was found in but 41 (3 per cent.) of the author's cases.

Typhoid Fever.—Opinions differ as to the frequency of tuberculosis following typhoid fever, as the diseases are frequently confused, the diagnosis of typhoid often being made at the onset of tuberculosis. No certain relationship has been established. A history of typhoid fever was given by 74 (4.2 per cent.) of the writer's patients.

Malaria is a frequent history obtained from tuberculous patients who reside in malarial regions. Such was given by 49 (2.09 per cent.) of the writer's series. Its actual etiological position is much exaggerated by the confusion of the symptoms with those of tuberculosis.

Injuries.—*Trauma* is important in creating favorable conditions for infection or spreading that which may be present. The ruptured blood-vessels and extravasated blood arrest the bacilli, which may enter the circulation, and hence form the nidus for infection after contusions. Joint, pleural, and meningeal tuberculosis is very naturally associated with injuries in the popular belief, and quite justly. Blows on the chest

are considered equally important in connection with pulmonary tuberculosis. Five of the author's patients gave a history of blows on the chest and two of falls. Concussions and nervous shocks, such as are produced by falls and railroad accidents, should have a place in the etiology of tuberculosis. The relationship of injuries in athletic contests to subsequent tuberculosis demands study. Surgical operations upon tuberculous glands and joints are occasionally followed by dissemination of the infection. In 18 of the author's patients, surgical operations (13 being for appendicitis) appeared to play a predisposing part.

Environment.—*Climate.*—The predisposing influence of low, damp climates was greatly overestimated in former times, because of ignorance of the essential infection. At the present day the opinion has reached the opposite extreme, that no importance is directly attributable to this element in man's surroundings so far as tuberculosis is concerned. The truth, doubtless, lies in a mean between these extremes. The debilitating heat of the tropics, with its high humidity and the depressing effect of the fogs and wet winds of the Atlantic coast, must only be contrasted with the invigorating highlands of the interior and the arid deserts and sunny table-lands of the far West to admit that climate is a potent factor in physiological resistance to tuberculosis. On the other hand, that it can be a specific predisposition is no longer claimed, for in the statistics adduced to show this, too many uncontrolled factors entered which are of much greater importance. Gordon, of England, has apparently demonstrated, by comparison of countries otherwise similar in race, occupation, etc., that wet winds increase the mortality of tuberculosis. It is further believed to be more acute in hot climates. No exemption from the disease is found in any climate when the other conditions for infection and development of the disease are present.

Density of Population.—The prevalence of tuberculosis is universally greater in cities than in rural communities, and no more constant factor is brought out by statistics. This fact is, however, bound up with so many conditions that it has little meaning taken by itself. The occupations and manner of life, together with the crowded dwellings of urban peoples, directly favor infection as contrasted with residents of the country; yet by absence of sanitation, country hovels may parallel the dangers in city tenements.

Occupation.—Certain dusty occupations especially predispose to tuberculosis. Stonecutters, quarrymen, metal and glass grinders and polishers are the most concerned. Organic dust is of less importance, yet acts deleteriously to some extent upon millers, woollen and cotton weavers, cigarmakers, etc. *Noxious gases* also depress the health and irritate the air passages of smelters, chemists, and foundrymen. Extremes of heat and cold act similarly upon bakers, stokers, and plumbers. Ascher[1] has made a statistical and experimental study which indicates that smoke is also a directly predisposing factor, but the tuberculosis mortality statistics of the mill towns in America, such as Pittsburg, do not confirm this view. The *sedentary* employments, such as book-

[1] *Der Einflus des Rauches auf die Atmungsorgane*, 1905.

keeping, clerking, and other mental as distinguished from physical occupations, act more indirectly, by reason of long hours of confinement in a sitting or stooping posture, added to nervous strain. Out of 1947 private patients recorded with some occupation, the writer found 316 clerks and book-keepers, 147 students, and 97 teachers. The subject is so complicated with all the other things that make for ill-health that the prevalence of tuberculosis in any given occupation is not a certain index of the harmfulness of the calling itself. For example, persons of weak physique are more likely to select indoor sedentary employments which are not necessarily predisposing to vigorous persons.

Bad habits contribute a most powerful predisposition. Alcoholic excess is a frequent history among the tuberculous who are otherwise free from obvious predisposition. Tobacco and drug habits are less clearly predispositions, but lessen nutrition and the defensive powers. Masturbation, sexual excesses, and perversions favor infection by weakening the nervous energy and vascular tone. A considerable proportion of tuberculous males of good physique give a history of gonorrhœa and alcoholism. Irregular and insufficient sleep, extreme exertion, mental or physical, also coöperate with depraved habits to bring about the disease in many otherwise resistant individuals. Of the writer's cases 94 (5.5 per cent.) gave a history of dissipation, and 174 (10.3 per cent.) of overstrain, frequently combined with the former.

Poverty.—No single element appears so important in the development of tuberculosis as this. Statistics of pauperism and consumption coincide in their variations; the causes that lead to poverty are potent in inducing this disease, and the consequences of poverty are yet more so, because crowding, squalor, poor and insufficient food, filth, and ignorance accompany the downward trend in humanity. Consumption is the social disease *par excellence* at the terminal stage of poverty. Körösi established for Budapest that among 10,000 living inhabitants, 40 well-to-do persons, 62.7 moderately well-to-do, 77.7 poor, and 97 paupers died of consumption. On the other hand, poverty as a *result* of family tuberculosis was found to be the reason for seeking charitable aid in 34 per cent. of 1600 families in New York City.[1]

Danger of Infection.— *Dwellings* which are crowded and poorly lighted and ventilated are the source of easy infection and form the chief danger to the poor in great cities. The "lung blocks" so graphically displayed by the New York Health Department and by the Phipps Institute in Philadelphia appear to show clearly how tuberculosis predominates in the most crowded sections of those cities. Besides the close contact of individuals, the air of the rooms is greatly vitiated, and the excessive heat and moisture debilitate the inmates. The classic experiments of Trudeau on the fatal effect of cramped and poorly ventilated quarters on tuberculous rabbits, as compared with the recovery of those permitted to live in the open, directly illustrate the baneful effects of crowding.

Family.—Tuberculosis is so largely a family disease, with from 40 to 60 per cent. of all patients disclosing a history of others in the house-

[1] Kingsbury, *Medical Times*, 1912, xl, 373.

hold, that the importance of family infection can hardly be exaggerated. The opportunities are innumerable in the homes of the poor and rarely wanting among the wealthier classes. The danger to children is of first importance because of the ease with which infection occurs at this period of life; while adults are usually brought into a condition of susceptibility by illness, depressing care, and solicitude for the consumptive relative, besides the vicissitudes of life in general which fall heavily upon consumptive families.

Marriage.—The influence of marriage or of married life in relation to tuberculosis has been studied carefully, and the danger of infection of husband or wife appears relatively far less than for the children. The percentage of cases due to infection between the partners in marriage is given as high as 23 per cent. by Cornet, but others attribute only 3 to 6 per cent. to mutual infection. Cornet's figures are from very poor people, the others from better-situated families. There are serious doubts, however, of the value of these observations when careful statistical methods are used. In E. G. Pope's[1] study of marital infection no definite proof was found to support the theory of infection between married persons. Mortality statistics have indicated a generally higher death-rate for widows and widowers from tuberculosis than for the single at those ages. Weinberg finds that the surviving partners of the tuberculous have twice the mortality from tuberculosis that is found in the general population at the same ages. Many other factors play a part, and the disease is actually less prevalent among the married than the single, "partly due to the fact that marriage in itself is more or less a process of natural selection, and partly to the greater regularity and soberness of life induced by marriage" (Mayo Smith).

Factory or Shop.—Formerly these places were nearly always unsanitary, poorly lighted, scantily heated, and without ventilation, all of which contributed to the danger of infection. In the large cities these conditions still prevail to a great extent, and the consumptive workman can unquestionably communicate the disease to his fellows if they are in close quarters and he is careless with his sputum. Clerks, salespeople, and employees in public offices in which many persons congregate are not only exposed to their tuberculous fellow-employees, but to visitors who may bring the infection directly by coughing, spitting, or indirectly from their hands, handkerchiefs, clothing, etc. We may not believe, as Cornet states, that a consumptive workman is a greater danger to his fellow-workmen than to his family, for if he is so careless in his habits at work, he is likely to be so at home, where the far more susceptible children are exposed. On the other hand, it may well be true in the exposure of the child laborer, that disgrace of civilization the sum of whose disease and misery will never be fully known.

Institutions, Sanatoriums, and Health Resorts.—A great deal of divergent evidence exists for and against the danger of hospital infection for the employees, physicians, nurses, and attendants. Cornet relates that among the Catholic hospital nursing orders 62.88 per cent. died of

[1] *Drapers' Company Research Memoirs,* 1908, vol. iii.

tuberculosis in the cloisters during twenty-five years, according to a government inquiry, which included 74,306 persons. On the other hand, the record of special hospitals and sanatoriums for tuberculosis is quite the reverse, as in the case of the Brompton Hospital in London (Theodore Williams). Moreover, no case of tuberculosis has been known to develop among the employees of the Adirondack Cottage Sanitarium since its foundation, twenty-eight years ago. These included waitresses, chambermaids, and laundresses, many of whom were badly nourished on entering the service.

From these contradictory experiences it is evident that there are marked differences in the hygienic conditions and control of the patients, whose habits largely depend upon their intelligence and station in life, or else entirely false inferences have been derived from incomplete data. In the consumptive wards of general hospitals the presence of bacilli has been repeatedly demonstrated in the dust, and Strauss found them in the nasal secretions of one-third of the physicians, nurses, and other attendants at the Charité Hospital in Paris. There can be no doubt, therefore, of the possibilities of infection of susceptible individuals in these institutions. It has been thought that the presence of tuberculous patients in general hospital wards endangered the other patients, and instances are cited in recent literature in which convalescing typhoid and pneumonia patients subsequently developed tuberculosis. While these have only the value of circumstantial evidence, the separation of consumptives from such patients is logically demanded.

Of late much fear has been excited about the danger of infection to the residents in *health resorts*. No foundation for such fear has been demonstrated in any American resort, and the most unbiased investigations have even proved the contrary, for relatively fewer cases of tuberculosis develop than among other communities not resorted to by the tuberculous. Several factors tend to obviate danger, such as the generally open-air life of the invalids, who are as a rule intelligent, and have comparatively little indoor contact with the residents. Furthermore, the disease is usually properly recognized and some precautions instituted, whereas these are often delayed at home or concealment is purposely practised.

Prisons and *asylums* have furnished a harvest of tuberculosis in the past. Villemin noted that the mortality from this disease was three times as great in the French prisons as among the free population. Quite similar records have held good for other countries. The deaths from tuberculosis in the Eastern Pennsylvania State Penitentiary from 1878 to 1902 were 60.8 per cent. of the total mortality (Hinsdale). In the New York State prisons 75 per cent. of the deaths were reported as due to tuberculosis in 1890 (Ransom). It is far from clear, however, that contagion is especially frequent, since so many prisoners are already infected on admission, and the confinement and depression of prison life favor the progress of the disease.

Schools.—The question of school infection has received attention of late in increasing degree. Many teachers have the disease in an open form, and while their contact with their pupils is relatively less than

that of the parents, it constitutes a real danger. Because pulmonary tuberculosis is infrequent in childhood, the infection from fellow-pupils is not a frequent risk. Tuberculosis is, nevertheless, present in a large number of public school children, as revealed by the modern inspection in vogue in some cities. In an investigation at Cleveland, Ohio, 7.5 per cent. of 504 children of tuberculous families or exposed more or less intimately to a tuberculous individual were found to have some form of the disease; 12.6 per cent. were suspected (Lowman).[1] Grancher has discovered similar conditions in Paris. Among 4226 school children 15 per cent. were deemed to be certainly tuberculous or strongly suspicious. The minimum estimates are appalling enough, but speak stronger for family infection than for the exposure in school.

Infection.—Historical.—The reference to the belief in contagion by Aristotle and Galen has been mentioned, and every century had writers who recorded their opinions that consumption was infectious as well as transmitted from parents. The leaders in medical thought, Morgagni and Valsalva, excited the public fear to such an extent during the eighteenth century that drastic laws were enforced in Italy providing for isolation of consumptives, notification by physicians, and destruction of the clothing and effects of consumptives (Naples, 1788). The extreme fear of contagion which was prevalent and still is a part of the folk-lore in southern Europe has reappeared in the bacterial era, fortified and exaggerated by half truths in the minds of intelligent people.

During the early part of the nineteenth century the belief in contagion was lessened by the influence of Bayle and Laennec, who emphasized tuberculous diatheses, predisposition, and heredity, although admitting contagion in some instances. The pathologists focussed attention upon the morbid changes in the tissues and the inheritance of this disease became a firmly fixed belief among all classes of physicians. Virchow's teaching still further separated the idea of infection from tuberculosis because it uprooted the belief in the unity or specificity of tuberculous caseation and the identity of scrofulosis and tuberculosis. He believed in an inherited and acquired predisposition, which required no mysterious contagion to excite the disease. These ideas were dominant when Villemin's discoveries led to joint investigations by physicians to determine, if possible, evidences of infection. When, therefore, Koch's discovery was announced, much attention was given to the possibility of the direct transmission of the bacillus from parent to offspring. Baumgarten has to the present time persistently maintained this to be the chief source of tuberculosis in spite of accumulated evidence for the importance of external infection.

The notable studies of Cornet next indicated the probable mode of infection to be from the dust of infected rooms and surroundings of consumptives; this formed the basis for the modern prophylactic measures for the disposal of sputum and disinfection of apartments. When the inhalation of sputum-dust had about achieved universal recog-

[1] *Transactions of the National Association for the Study and Prevention of Tuberculosis*, 1907, vol. iii.

nition in explaining infection, Flügge and his associates introduced strong experimental evidence of moist "droplet" infection, by which theory the predominant danger was attributed to the presence of a hard-coughing consumptive. Lastly, v. Behring has introduced the more revolutionary idea that in most cases the infection is derived from milk and begins in infancy through the intestine, and often from bovine sources. Amid all the confusion and readjustment of ideas in progress, it is small wonder that a general dread of any contact with tuberculous persons has steadily increased, in spite of definite knowledge of the sources of danger and the measures to combat it.

The Sources of Infection.—The human sputum is the greatest factor in the dissemination of bacilli, whether by direct transmission in the moist condition or indirectly through the medium of dust in contaminated rooms, or of food, clothing, and other objects. Many millions of bacilli are contained in the consumptive's sputum, and a large proportion of them are capable of growth when first discharged, judging from the culture experiments of Hesse, with sputum directly upon agar, and contrary to the former findings of Kitasato.

The milk and flesh of tuberculous cattle have long been regarded as sources of danger, but convincing proof of this has been difficult to obtain. That this is now entirely satisfactory may be confidently asserted. The sensational denial by Koch in 1901 of any serious importance from bovine infection for human beings led to an industrious study of the subject throughout the world, and to the creation of two governmental commissions (Germany and Great Britain) for this purpose. Both have rendered reports which confirm the earlier findings of Theobald Smith and Ravenel in the United States, who detected bacilli of bovine type in the mesenteric nodes of infants. The United States Bureau of Animal Industry has also conducted valuable experiments, all tending to show that bovine infection is not unimportant for man. The number of cases with strongly presumptive evidence of bovine origin is nowhere so great as to compare in importance with the human source; but if it should later be demonstrated, as suggested by v. Behring, that the bovine type of bacilli may undergo a transformation of virulence by long residence in the human body, so that they are indistinguishable from the human types, the statement would require modification. The studies on virulence have at least suggested many intermediate types. In America bovine tuberculosis is a relatively small factor in the causation of the human disease, because it is relatively infrequent,[1] while in Japan it is entirely wanting, according to Kitasato, because not only is no milk used by the mass of people, but the few cattle in that country are free from tuberculosis. The same conditions concerning the use of milk are alleged to exist in Greenland

[1] In the extensive study of this subject on unselected cases in New York City by Park, Krumwiede *et al.*, at the New York Board of Health Research Laboratory, a large number of bovine infections in children were discovered (*New York Board of Health Research Laboratory Collected Studies*, vols. iv, v, vi, 1908–9–10). They estimated that from 6¼ to 10 per cent. of deaths from tuberculosis in young children are from bovine sources.

(Djier), the Gold Coast (Fisch), China, the Philippines, Turkey, Sicily, and Sardinia; yet in all these countries tuberculosis is prevalent in all forms, and to the same extent as in Europe and America.

On the other hand, it is thought to be of great moment in the British Isles and European countries by Raw, Woodhead, and v. Behring, and is shown to be a factor of importance by the reports of the British and German Commissions. Tuberculosis in swine, sheep, goats, and the smaller domestic animals is a practically negligible danger, owing to the comparatively slight use of uncooked flesh and the infrequency of the disease among them, as well as in the parts of the animal used for food.

Hereditary Transmissions.—The ancient belief in the direct inheritance of the disease dies hard in spite of the weight of evidence against it as a frequent source. The direct transmission of tuberculosis involves the transfer of the bacillus in one of several ways: (1) From the father through the seminal fluid or by means of the spermatozoa; (2) from the mother through the ovum or placental blood. Evidence for the paternal transmission rests on the positive findings of tubercle bacilli in the human semen. The conception of an actual infection of the spermatozoa with the bacillus is quite out of the question from any facts in our possession. If bacilli succeed in penetrating the ovum from the semen, it is altogether probable that they must first infect the mother. All in all, there is no evidence, clinical or experimental, of a paternal transmission in the sense of inheritance. The infection of the ovum is equally doubtful before impregnation, although Baumgarten claims success in one rabbit's ovum artificially fecundated. It is more than likely that human ova in which tubercle bacilli might lodge would be unfruitful. Clinically, ovarian and tubal tuberculosis is uncommon, and a complication which usually interferes with impregnation.

Placental transmission is practically the only form of inheritance which merits attention, and this is, strictly stated, congenital infection from the mother. Exhaustive search has been made for cases of tuberculosis to support the inheritance theory, and a list of twenty has been collected by Schlueter, which are considered to have been undoubtedly derived from intra-uterine infection. Warthin and Cowie have made a special study of placental tuberculosis more recently. Not infrequently the bacilli have been demonstrated by inoculation with the fetal tissues when no signs of tuberculosis were evident in them; this has been used by Baumgarten as an argument in favor of his well-known theory of latency and insusceptibility of the infant tissues to the formation of the tubercle, owing to their great activity of growth.

The methods by which intra-uterine infection can occur are by the direct passage of bacilli from the blood of the mother to the fetus through a rupture in the vessel walls of the villi or by means of an actual placental focus from which bacilli may escape into the fetal circulation. The claim of Baumgarten for inheritance of the parasite and a dormant stage in its life-history is well combated by the relatively few cases in which the conditions are present for the transmission of the bacilli, and the acute course of infantile tuberculosis in general. Among 1005

surgical tuberculous patients between the ages of ten and fifteen years, Lannelongue found only three whom he could denominate congenital. Since the opportunity for external infection begins at birth in just these supposedly hereditary cases, we are not justified in regarding them as such; nor can we consider the inheritance of the bacilli an important factor in the conveyance of tuberculosis from parent to child. Atavistic inheritance of the bacilli from the grandparents is wholly inconceivable.

External Modes of Transmission.—The opportunity for receiving tubercle bacilli into the body from outside begins with birth and the means of transmission are numerous in infected surroundings. Cases are on record in which consumptive midwives are supposed to have infected infants by blowing into the mouth to start respiration at birth (Cornet). Inoculation experiments with the milk of consumptive mothers have been generally negative, as would be expected, since actual disease of the mammary gland is rare. Yet breast-fed infants can be easily infected by the sputum-soiled fingers of the mother, which are frequently in contact with the nipples or put into the infant's mouth. The same is true of the bottle-fed nursling, apart from the danger of bovine sources of infection. Perhaps next in importance are the fingers and toys of the creeping infant, frequently soiled from infected dirt of the floor as well as from the clothing, and especially the handkerchiefs of the consumptive mother or nurse. Bacilli have been found to be frequent on the hands (Dieudonné) and under the nails (Preisich and Schutz) of children in consumptive families. The use of handkerchiefs to receive the expectorated sputum or to wipe the mouth is quite universal among otherwise cleanly persons, and unquestionably constitutes a potent means of transmission, both in the moist condition and after drying. Contamination of the pocket, dress, or pillow is frequent by the customary method of handling handkerchiefs, but particularly affects the hands of the patients (Baldwin).

Bacilli are decidedly more virulent in the moist condition, and it is conceivable that the hands may convey them frequently from the parent to child indirectly by food, confectionery, drinking cups, door knobs, pencils, etc. The frequent use in common of spoons, forks, glasses, towels, etc., is also to be recalled. The contamination of food is also possible by means of the feet and excrement of house-flies, which have previously alighted on sputum (Spillman and Haushalter, Moeller, Lord); also by cockroaches (Kuster) and lice (Weber).

Sputum may be brought into houses on shoes and trailing garments, and by pets, especially dogs, which habitually lie upon the sidewalks and doorsteps; also, they may convey infection to children by their habits of indiscriminate licking. It is an open question whether the inhalation of sputum dust from floors and clothing or the moist spray from the cough constitutes the most serious danger in childhood. The deep inspirations of the crying infant give the opportunity, it is true, but the infection in this form is likely to be less than in the other modes.

We know through the numerous examinations of dust that it is a means of transmission, but the bacilli have but limited vitality when dry, and as new conceptions of infection have come to view, the role of

dust diminishes in seriousness. The demonstration by Flügge that moist particles of sputum were coughed out so impalpable as to float in the air some minutes, and could be inhaled, brought out a factor formerly recognized by Cornet in his experiments, but not sufficiently valued. In view of the remarkably ingenious experiments which support each side of the controversy between these experimenters we must assume that both modes of infection are of some importance. The danger of so-called *droplet-infection* results chiefly from expulsive coughing, but may occur in hawking, loud talking, laughing, singing, and sneezing. Ordinary breathing carries no infection.

How little danger there is for adults even when directly exposed to the cough, spray, and dust is shown by the investigation of Saugman. Among 174 previously healthy sanatorium physicians whose average service was three years, and who were followed three and one-half years further, but 2 developed tuberculosis; among 64 laryngologists from eight clinics, none were affected during or after their service. Considering the close contact with patients and frequent demonstration of bacilli on the head mirrors and even in the nasal mucus of physicians (Straus, Moeller), the record is noteworthy, and evidence against the frequency of adult infection as well. The act of kissing on the lips may be a danger to children, though for adults this is probably overestimated in the popular mind.

Some other means of transmission are suggestively possible, but of exaggerated importance in the lay mind as far as evidence goes. Such are the blankets of sleeping cars; telephone transmitters; money, particularly paper currency, and library books. It may be admitted that in some instances young children are endangered in these ways, but it is doubtful if adults undergo danger worthy of mention.

Paths of Infection.—It has been customary to consider three distinct modes of primary infection in tuberculosis apart from inheritance, in accordance with former theories of the reception of the bacillus into the body. These were by (1) inoculation, (2) inhalation, and (3) ingestion. Since changed conceptions have been introduced, and the probability that combined inhalation and ingestion make the mode of infection from the exterior less simple than the above division implies, it seems more useful to make the distinction only between the three kinds of surfaces exposed to invasion from without, namely, (1) the cutaneous, (2) the mucous membranes, and (3) the pulmonary alveolar. By this division all sources of infection are recognized and included without undue emphasis being placed on any one mode. That it has not been a simple matter to establish the exact path of entrance of the tubercle bacillus into the human body is evidenced by the mass of experimental work devoted to the problem through many years, out of which disputes and confusion have arisen and still reign.

Cutaneous Inoculation.—Infection through the external skin is of slight importance in the production of generalized tuberculosis. The conditions are not favorable for an easy proliferation of tubercle bacilli in the skin itself, possibly because of deficient nutriment and the insusceptibility of the skin epithelium. The mere rubbing of tubercle

bacilli under the skin is insufficient to infect adults, but abraded surfaces, especially in children, are occasionally the starting-points of fatal infection. Inoculation tuberculosis is for the most part localized at the site of the wound or at most spreads only to the nearest lymph nodes. It is seen frequently on the hands of pathologists and bacteriologists, and it is surprising that more serious results do not follow. Laennec himself, in 1799, received an inoculation on the hand and died of pulmonary tuberculosis twenty years later. It is doubtful from the evidence available that there was any causal connection between the two events, although Villemin cited this as an illustration of the inoculability of tuberculosis. It must be remembered that most adults obtain some infection early in life, which acts to a certain extent as a protection against subsequent exposures. Nevertheless, man is certainly quite resistant to cutaneous or subcutaneous infection, considering by contrast the ease with which susceptible laboratory animals develop progressive tuberculosis from slight inoculations into the skin. Many instances of cutaneous inoculation are recorded in the literature: the cuts from broken cuspidors and chamber vessels; from ear-rings; from splinters in an infected floor into bare feet; from the operation of tattooing; in performing circumcision; from scratches with infected fingernails; also of the nose and by the use of handkerchiefs previously used by consumptives. Bruns has collected five cases produced by hypodermic injection, three of whom were morphine habitues (Cornet).

Infection of the nasal fossæ and corners of the mouth and eyes not rarely leads to lupus of the face; many of these lupus subjects also have tuberculosis elsewhere which is the source of the infection. Autocutaneous infection is rarely produced, considering how frequently the hands and nails are soiled with sputum.

Vaccination was formerly regarded as a possible source of danger, but the modern use of calf lymph with the precautions taken in its preparation leaves no basis for fear. Calves employed for producing vaccine are proved free from tuberculosis by the tuberculin test. The comparatively mild effects of accidental or intentional subcutaneous inoculations (Baumgarten, Klemperer, Kleine) with bovine bacilli have been used as proof of the relative harmlessness of bovine bacilli for man, with questionable propriety, in view of the fatal results of such infection through the intestinal channel, and the instances of even progressive disease ascribed to skin infection (Ravenel).

Primary inoculation tuberculosis is, nevertheless, not often recognized, if indeed it occurs frequently, as believed by some, from abrasions in the mouth and tongue, such as are produced by carious teeth or after their extraction, and following operations upon the nose, nasopharynx, larynx, and tonsils. Still rarer are instances of genital, rectal, and conjunctival infection from injuries. It would be surprising how infrequently infection apparently results from lacerations in the mucosa, which leave an open door for tubercle bacilli with conditions favorable for absorption, were it not evident that the virus is not universally present and not always in a virulent condition.

In youngest infancy and childhood, however, abrasion of the gums in

dentition and the coincident transport of bacilli from dirty fingers, both of the child and mother, into the mouth, may lead to infection, as emphasized by Volland and Westenhoeffer. The same is true of the habit of picking the nose. How often infection actually occurs in these ways has never been ascertained, since it is well recognized that the portal of entry may not show signs of disease, especially in infancy. The experiments of Weleminsky, Harbitz, v. Behring, Bartel, and others, in which living tubercle bacilli were demonstrated by inoculation of lymph nodes into guinea-pigs when no signs of disease were present in the nodes, indicate the possibility of an unsuspected path of entrance, especially in children in whom no trace may be seen at the site of infection. On the other hand, the objection made that sooner or later the regional nodes would show the disease if infection really occurred, is a strong one, and on this basis statistics of lymphatic tuberculosis about the face and jaw do not favor great frequency for traumatic infections in those regions.

It is quite as accurate to consider this as *infection* by *absorption*. The readiness with which the glandular and especially the adenoid tissues of the nose and throat become the seat of transient infections has long furnished an argument in favor of this pathway also for tuberculosis (Aufrecht, Freudenthal). When pulmonary tuberculosis is present, secondary disease of the faucial tonsils is very common, yet primary tuberculosis of these structures is comparatively rare.

Jonathan Wright, Broca, and many others have made microscopic examinations of "adenoids," with generally negative results. Cornet's summary of 1745 cases gave 4.1 per cent. of positive results. Primary tuberculosis of the faucial tonsils is less rare, but closer observation of late and inoculations of all these tissues have revealed latent bacilli present more frequently than hitherto suspected (Dieulafoy, Lartigau and Nicoll, Harbitz). Submaxillary and cervical nodes are so frequently enlarged in children from pyogenic infections that the decision as to the frequency of primary tuberculous infection of this lymph system is by no means easy.[1]

This fact demands more attention because of the more important studies in recent years (MacFadyean and McConkey, Spengler, Walsham, and others, but especially by Harbitz), which by more careful microscopic examination combined with inoculation tests have disclosed the fact that lymph nodes presenting nothing but simple hypertrophy or even normal appearances may contain virulent tubercle bacilli without other evidence of tuberculosis. It is disquieting to note that Harbitz found them most frequently (13 out of 18 cases) only in the cervical group of nodes and in the youngest infants, mostly less than a year old. These are significant facts bearing upon the absorption of bacilli from the mouth and nasopharynx. Whether lodgement or retention of tubercle

[1] Volland estimated that 94 per cent. of children between the ages of seven and twelve years had enlarged cervical nodes. Neumann summarized 4883 children between one and nine years, of whom only 6.38 per cent. had presumably tuberculous enlargement of the nodes, while Laser considered 32.4 to 58.9 per cent. of cervical enlargements tuberculous in 1216 school children.

bacilli in these nodes for a time necessarily implies infection or not is a question yet more difficult to decide. Nearly all the dust that is inhaled is caught in the nose, or, during mouth-breathing, in the mouth or pharynx. The coarser particles of dust are soonest deposited, and normally cast off by the mucous flow and movement of cilia in the nose or frequently swallowed from the pharynx. Relatively little reaches the larynx, trachea, and bronchi by direct inhalation or is aspirated secondarily from the nasopharynx and mouth.

Localization of tubercle bacilli in the mucosa of the lower respiratory tract is rare as a primary disease so far as pathological studies have revealed, although it is by no means certain that bacilli do not frequently pass through into the adjacent lymph nodes and produce the first recognizable changes in the lung hilus and bronchial nodes.

The gastro-intestinal tract has been brought to the front in recent years as the most important pathway of entrance. While a few pathologists long ago held to the idea of ingestion infection from their successful feeding experiments, the weight of evidence seemed to be in favor of lung infection. Nevertheless, v. Behring aroused the question anew in 1902 by announcing his conviction that food infection accounted for all the results of previous experiments, questioning the validity of Cornet's and Flügge's interpretations, and presenting his own observations that lung tuberculosis was primarily of intestinal origin and from infected milk. This revolutionary idea has found slow acceptance, but has led to many new experiments with partly confirmatory results, and to a pronounced modification of the theory of primary infection by way of the pulmonary alveoli, since careful pathological studies have been made of the earliest signs of infection in the lymphatic system (Harbitz, Weichselbaum, Mallory and Wright, and others). It is only necessary to mention here that v. Behring and Roemer have demonstrated the easy permeability of the stomach and intestinal mucosa of the newly born animal for bacteria and unchanged protein. Later in life the passage of bacilli is favored by erosions due to catarrh or other abnormal conditions and diseases. The bacilli may pass directly into the blood through the thoracic duct, or be arrested in the mesenteric nodes in primary infection without a trace of their site of entrance, but they tend to localize in the mucosa and Peyer's follicles if a previous infection has created a susceptibility. Baumgarten maintains that a focus is always produced sooner or later at the point of entrance, although it may be microscopic. Many recent experiments have shown that the bacilli can pass into or between the intact epithelium, and can be traced step by step to the mesenteric nodes or thoracic duct, chiefly from the lower part of the ileum or cecum; the stomach is rarely penetrated except in newly born animals.

The demonstration of primary mesenteric node infection in young infants, and adults as well, without other signs of the disease (Harbitz), leaves no doubt of the possibility of intestinal infection under some conditions. The only questions at present mooted are: (*a*) Their frequency compared to the respiratory route; (*b*) the relative number of bacilli needed, *i. e.*, the dose, since Flügge claims to have shown that

vastly more are required in feeding experiments than by inhalation; (*c*) finally, the important matter of its relation to pulmonary tuberculosis is yet unsettled.

Infection of the genito-urinary tract and conjunctiva is, so far as known, or at least proved, of traumatic origin when from the exterior, and too rare to deserve special consideration.

Pulmonary Alveolar Infection.—The most important fact in favor of this theory is the presence of pigment in the cells themselves or in the interstitial spaces, especially under the pleural surface. The convincing experiments of Arnold remain today the chief foundation for the inhalation theory, in spite of attempts to show that pigment can be deposited in the lungs after feeding experiments. When carefully controlled, such experiments have produced quite opposite results (Bennecke, Aschoff). Hence, the deposit of coal-dust and stone-dust in the lungs of miners, etc., cannot be interpreted at present in any way but by inhalation directly into the alveoli or small bronchi. It must follow logically that the bacilli in the form of fine dust must also lodge there, and be carried into the subpleural and interstitial spaces, as is true of anthracosis. The problem seems simpler at first sight than it really is, because the very earliest changes in the inhalation-infection experiments are not usually in the alveoli, but in the lymph nodes, probably from mucous membrane absorption, since obviously less inhaled dust or spray penetrates as far as the alveoli. Moreover, the great frequency of bronchial lymph-node tuberculosis before any discoverable changes in the lungs, especially in children, and the greater permeability of the lymph spaces at that age, have thrown doubt on former theories of the mechanism of primary infection. This mode of lung infection is accomplished by way of the bronchial glands in most cases which receive the lymph from a large area and pass it into the blood very directly, thus carrying the infection to the small capillaries in the alveoli, where they lodge. Hodenpyl, in 1899, decided that the subpleural pigmented nodules so frequently found were often tuberculous when no other focus was discoverable, and Ribbert has recently accepted the same view, but thinks the deposit of pigment generally precedes and aids the retention of tubercle bacilli by clogging the lymph spaces and minute subpleural lymph nodes.

Moreover, Schroeder and Cotton have ingeniously produced pulmonary tuberculosis in calves by inoculations into the tail as well as by feeding experiments. It is therefore maintained that the lung capillaries act preëminently as a filter for the blood and lymph circulation, and indirect infection frequently occurs by way of the intestine, mesenteric nodes, or thoracic duct, thence to the blood stream and lungs.

A modified opinion is therefore necessary at present in reference to the frequency of directly inhaled primary infection of the alveoli, in that it is less frequent than formerly supposed.

Relative Frequency of Modes of Infection.—The weight of opinion was in the past in favor of the lung as the most frequent pathway, because the statistical comparisons of cases of supposedly primary lung and bronchial node disease were far in excess of those in the intestine and

mesenteric nodes. The estimates vary greatly, however, ranging in the case of primary intestinal invasion from 2 to 30 per cent. Such differences were largely due to the failure to make a careful study of the very incipient stages or latent forms in the lymph nodes on the part of the older observers and the absence of microscopic and inoculation tests. When the later work of Councilman, Mallory, and Pearce, Harbitz and Rosenberger is examined, it is seen that the bacilli are much more frequent in the mesenteric nodes than was supposed. How often they go on to the production of actual disease may still be an open question. At present the figures suggest that one-fourth of all cases of tuberculosis, in children at least, receive the infection by way of the gastro-intestinal route, either simultaneously with or independently of other ways of entrance. Altogether the knowledge now available tends to lessen the importance of primary inhalation infection through the bronchi and alveoli, yet it by no means places it second to other channels. There is some reason to think that below the age of fifteen years infection by other channels is more frequent and perhaps preponderant by way of the digestive tract, and localizes in the lymph nodes at first; yet the possibility of simultaneous inhalation and ingestion infection prevents a certain conclusion. In adults the first focus of disease is more often at the portal of entrance, which supports the inhalation theory for the origin of pulmonary phthisis in the majority of cases, whether it be primary or so-called "superinfection." Furthermore, the greatest proportion of latent or healed tubercles found in the lung apices coincides with the increased age of such individuals, and is best explained by inhalation infection.[1]

Latent Infection.—This expression is intended to apply only to the presence of the disease-producing agent in the body without actual tubercle formation, a true "pretuberculous" stage of the disease.

Baumgarten has long stoutly maintained that bacilli could be inherited and rest for long periods in the body, restrained by the active tissue growth of the infant. There is little reason to think this to be true, as already explained. Tubercle bacilli have been found in the lymph nodes without apparent effect on them except to produce a slight hyperplasia; at least, specific changes may be absent for some time (Loomis, Manfredi and Frisco, Harbitz, etc.). Bartel and Neuman, by means of feeding experiments in rabbits, found that living bacilli could be present one hundred and four days in the nodes without specific changes, and finally disappear without leaving traces. Von Behring regards mild infections in childhood as predisposing or immunizing to later infection according to their severity. From what is known of the biology of the bacillus the probabilities are that virulent bacilli go on to growth and tubercle formation within a few weeks, and that less virulent strains

[1] Von Behring maintains that secondary tuberculous infections tend to localize at the point of entrance because of a susceptibility acquired from the first infection, thus accounting for ulceration in the lung and intestine found in adult life. He believes that the condition of susceptibility corresponds to that known as "scrofulosis" when well established. This theory has an experimental basis and clinical support in the greater frequency of superficial ulcerations in adults as compared with children, and the large number of persons who show susceptibility to tuberculin.

may remain alive several months, and eventually die with or without traces of their presence being left.

Reinfection.—*Auto-infection.—Cumulative or Additional Infection.*—In an individual previously infected with tuberculosis we know that tuberculin susceptibility may exist for a long time after clinical healing has occurred. It is, therefore, of interest to know whether such persons are capable of further infection from a source outside the body. The matter is very difficult to investigate, and the proof quite circumstantial when relapses in healed pulmonary tuberculoses are referred to a fresh infection. Experimentally, reinfections are not easily produced in animals, yet successive infections are usually assumed to have occurred in persons who have had a history of healed lymphatic tuberculosis in childhood (Cornet).

If future experiment and observation demonstrate that a primary infection is sufficient to account for the source of all subsequent developments of the disease, which position v. Behring holds, it would be more in keeping with the results of experimental immunity studies. On the other hand, cumulative infection in tuberculous families seems impossible to deny in young children under repeated exposure. More evidence has been brought of an acquired immunity by early infection (Roemer,[1] Hamburger), yet it must be remembered that overstrain may inhibit the protective mechanism and spread an old infection, while a fresh one may be admittedly possible under such conditions.

Frequency of Infection in General.—As to the frequency of tuberculous infection in general, Naegeli's remarkable findings of 99 per cent. in 500 autopsies, and those of Burkhardt, who found 91 per cent. in 1262 sections, are doubtless too high for the general population, since the material was taken from hospitals in manufacturing cities (Zurich and Dresden). Further objection is made that many of the cicatrices, adhesions, and chalky foci assumed to be remains of tubercles were in reality not such or may have been caused by dead and weak virulent bacilli. The percentages estimated by most pathologists, who usually regarded only gross appearances in determining tuberculous foci, vary between 30 and 60 per cent. of all sections. Probably the recent estimate of Harbitz from 50 to 70 per cent. for all ages represents an approximation of the truth.

An effort has been made to reach conclusions as to the frequency of tuberculosis by the tuberculin and agglutination tests. While the figures obtained by Beck (tuberculin) and Romberg (agglutination) correspond in a general way to postmortem findings, too many disturbing factors impair their value. The cutaneous and conjunctival tuberculin tests have been more recently used on so large a number of persons that doubt is no longer possible of the almost universal infection of city dwellers after the age of fifteen years.

Summary of Present Views on Infection.—It is highly desirable to arrive, if possible, at some definite conclusions and compare them in relative importance. In the first place, the doctrine of inherited or

[1] *Beit. z. Klinik. d. Tuberk.*, 1912, xxii, 301.

acquired susceptibility still holds sway except that a specific susceptibility is in doubt, and at most not common; next, that all infants are susceptible, and that susceptibility lessens with increasing age; lastly, that adults are comparatively insusceptible when without general or local lowered resistance and repeated or prolonged exposure. As to the sources of infection, the consensus of opinions and ascertained facts point to the sputum as of overwhelming importance, and that in certain cases, and especially in restricted areas having a large percentage of tuberculous cattle, cows' milk is an important factor, the flesh of tuberculous animals being of minor importance; lastly, that the mother's milk, the urine, feces, or other excretions of tuberculous individuals are not frequent sources of the infection. In the means of transmission there is a growing belief in the greater importance of infected food—especially milk—for infants and children rather than for adults; that the food may be infected directly by coughing or by dirt and dust from the floor and hands; that fingers and many other objects that find their way to a child's mouth are dangers. To adults both dust and moist droplets are the direct carriers of infection more often than infected food. It is doubtful whether inhaled dust is as dangerous as formerly supposed, but equally doubtful that the coughed spray plays a greater part than dust when the menace to adults is being considered. Infection is not often received through the skin, but most frequently through the mucous membrane of the mouth, air passages, and intestine. Alveolar lung infection is doubtless primary in some cases, but is relegated to second place by some, in comparison with the upper air passages and digestive tract. Pulmonary tuberculosis is often secondary to the latent lymphatic form contracted in early life. The infection may be dormant a few weeks before exciting the formation of tubercles, may then die out and leave no trace, or progress to the stage of actual tubercles, and finally, after a prolonged incubation stage in the lymphatic apparatus, become distributed to various organs. It is uncertain that a second infection from outside the body is of frequent occurrence after clinical healing of pulmonary tuberculosis in adults; 50 per cent. of the general population acquire an actual implantation of tubercle bacilli at some time during life.

CHAPTER V

THE PATHOLOGY OF TUBERCULOSIS

By W. G. MacCALLUM, M.D.

The Effects of the Tubercle Bacillus on the Tissues.—The action of the tubercle bacillus on the tissues is in its essentials similar to that of most other infectious agents which give rise to inflammatory processes, and it seems that rather too sharp a line of distinction between these anatomical effects and those of other inflammatory irritants has usually been drawn. Nevertheless, the changes are sufficiently characteristic to be recognizable with a fair degree of certainty which is rendered complete by the demonstration of the bacilli in the tissues. The anatomical changes are not uniform, but may present rather widely different appearances according to the mode of invasion and virulence of the bacilli. All such altered tissues have, however, in common the tendency to undergo a type of necrosis with the formation of a caseous material.

Perhaps the most characteristic of the results of the invasion of the tubercle bacillus is the formation in the tissues of minute grayish and translucent nodules of firm consistence, the miliary tubercles, so-called from their resemblance in size to a millet-seed. So characteristic, indeed, were these thought to be that the disease and the bacillus naturally received their names from this circumstance. Such nodules vary a great deal in size, and it now appears that those which are truly miliary, that is, resemble a millet seed in size, are by no means the smallest or ultimate tubercles, which may be so small as to be just within the limit of vision of a practised eye. This variation is in some degree dependent upon the tissue involved, the most minute tubercles being frequently seen in the liver, while those in the spleen and kidneys are usually larger. They may occur embedded deeply in the substance of solid organs, scattered upon the surface of such organs, in the lining of cavities, or in the walls of vessels, or they may form part of a sort of granulation tissue which results from the activity of the bacilli. The tendency to their formation is very strong, so that in the tuberculous lesions which are apparently not of this nodular character, especially after they have reached the later stage in their development, abortive attempts at the formation of such circumscribed nodules are always recognizable, new tubercles being formed as the old ones are destroyed and merge into the caseous material.

In their fresh condition the tubercles are visible, or often more readily palpable, as rounded or ovoid or flattened granules firmer than the surrounding tissue, and pearly gray or at times almost entirely translucent. The translucence of the small tubercles persists for no great length

of time, for within a short period, usually two or three days only, after their formation a central spot of opacity, usually of grayish or yellowish-white color, appears which gradually increases in size, and when adjacent tubercles coalesce becomes confluent with that in the next nodule. This opacity indicates the beginning of the ultimate necrosis or caseation which so generally befalls the tubercles. Fresh miliary tubercles are, however, frequently found at autopsy, since their formation in most cases is a more or less continuous process, new crops of nodules appearing as the result of dissemination of the bacilli from the older foci. In certain instances—and these are the cases of *acute generalized miliary tuberculosis*—thousands of such tubercles appear simultaneously not only throughout the lungs, but thickly scattered throughout all the organs and tissues of the body, studding the surfaces, and roughening the cut surface of every organ by their prominence. These thousands of tubercles usually result from the wholesale introduction of the bacilli into the blood stream from an older focus which invades a vein or the thoracic duct, and the patients die before the individual tubercles have had time to undergo much alteration.

Finally, such minute tubercles may under certain conditions remain more or less translucent, and without undergoing any caseation become converted into firm fibroid nodules in which the characteristic structure of the fresh tubercle is lost and only a hyaline mass of dense fibrous tissue remains. This may be regarded as a process of healing.

Microscopically, the miliary tubercle in its fully formed state is composed of a roughly concentric mass of cells of elongated form, with long, oval, vesicular nuclei. These cells, which are quite closely arranged often in easily recognizable concentric layers, are usually designated from their form epithelioid cells. Among these cells, especially in the outer portion of the nodule, numbers of smaller cells are usually seen which are round and have relatively large, deeply staining round nuclei, cells which resemble very closely the lymphoid cells of the blood and are by most recent writers identified with those cells. All these cells are supported by a network or reticulum of resistant fibrils which can be demonstrated by suitable methods. Similarly a network of fibrin filaments can usually be rendered visible throughout the nodule by the aid of the Weigert stain. Many tubercles show no further striking elements in their structures, but in the majority the well-known giant cells described by Langhans and Schuppel also occur. These are huge masses of protoplasm quite irregular in outline and often drawn out into long processes which ramify among the surrounding cells. They are provided with a large number of nuclei, often ten to twenty or more, which are usually arranged at the poles of the protoplasmic mass and often at its periphery in a ring so as to leave a central area devoid of nuclei and faintly granular.

Tubercle bacilli may usually be demonstrated by the staining method of Koch-Ziel-Nielsen and its modifications, lying among the epithelioid cells or in the protoplasm of these cells or of the giant cells. No vascular supply whatever can be seen in such nodules. Whatever vessels or capillaries existed at the point where the tubercle is formed become obliterated

and disappear, and no new ones are formed among the new-formed cells. A colored injection of the vessels of an organ studded with tubercles, therefore, leaves the tubercles as white nodules which stand out prominently on the deeply colored background of the rest of the tissue. This circumstance probably aids in bringing about the subsequent necrosis of the mass, although by itself it would not suffice to cause the death of such a minute nodule which might absorb sufficient nutriment from the surrounding fluids to maintain the life of the cells. Much more important in this respect is the action of the poison produced in the tissue by the bacilli, which first causes degenerative changes and finally the complete destruction of the cells. The nuclei of the epithelioid cells shrink and become twisted and distorted, and often so change their position as to lie with their long axis radially placed. For a time such nuclei take a very deep stain, but later they lose all power of taking up the stain. There appears among them, sometimes involving first the giant cell, but usually rather the adjacent portions of the tubercle, an area of complete disintegration of the tissue, the cells being converted into formless hyaline debris and caseous material.

As stated above, the tubercle nodules by no means always maintain their isolated character, but commonly become confluent or *conglomerated*, so that instead of forming rounded bodies the distribution is usually such that little groups or mulberry-like masses of tubercles arise. In these masses the concentric arrangement of the cells is often somewhat disturbed and irregular, especially in the interior. Such confluent masses of tubercles may reach a considerable size, although usually not without undergoing the characteristic necrotic process, so that it is not uncommon to see in the spleen or elsewhere partly caseous tuberculous masses reaching a diameter of 1 cm. or more. Indeed, the so-called solitary tubercles are of a far greater size, sometimes even reaching a diameter of 4 or 5 cm. These are circumscribed masses of dense caseous matter surrounded by a capsule of distorted tubercles and tuberculous granulation tissue, which are apparently formed by the continued production and confluence of tubercles with degeneration and caseation of those more centrally placed. They appear most frequently in the brain, and may constitute a tumor which by its bulk gives rise to disastrous consequences.

The common fate of the tubercle is caseation or necrosis of the more central portion. If sufficient time has elapsed perhaps the only exception to this is the conversion of certain small tubercles into a hyaline fibroid tissue, the fibroid tubercles mentioned above. The fact that a thin layer of living tuberculous tissue always remains about such caseous masses is probably due to the continuous extension and new formation of that tissue; nevertheless, it, too, is constantly encroached upon, leaving only ragged, distorted remnants of confluent tubercles.

The consistence of the caseous material varies in different cases, being sometimes very soft or semifluid, at other times firmer or of the consistence of cream cheese, while as time advances it may become dry and friable, or, when there is a deposit of lime salts, mortar-like. Further inspissation and the continued deposit of calcium leads with great frequency to the complete conversion of the caseous material into a

stone-like substance, which is then practically an innocuous foreign body as far as the host is concerned. These changes, which tend toward the solidification of the caseous substance, indicate a diminution in the activity of the tubercle bacilli; the destructive process ceases to advance and the mass gradually becomes encapsulated by a growth of granulation tissue just as in the case of any other foreign body. This encloses it completely and walls it off from the surrounding tissue, so that any remaining tubercle bacilli are imprisoned. Such encapsulated caseous nodules, sometimes as large as a cherry, are not uncommonly found in the lungs. The capsule is firm, hard, and deeply pigmented with coal and blood pigment, and the whole structure contracts until the nodule, even if it be not calcified, acquires a great degree of firmness. Anatomical evidence that a reinfection of the surrounding tissue may arise from such a nodule after it has become firmly encapsulated is very unsatisfactory, and in the cases of a renewed flaring up in an apparently healed focus, the new infection is probably not from any such healed lesion as just described, but rather from a still active though latent focus or from a new infection from outside.

The lodgement of tubercle bacilli in the tissues is not, however, always followed by the formation of definite tubercles alone. Frequently, especially on free surfaces, the formation of an abundant granulation tissue is associated with such tubercles. This tissue is highly vascular, and may be distinguished from ordinary granulation tissue not only by the presence of tubercles recognizable by their form and structure, but also by the abundance of epithelioid cells, identical with those which compose the tubercles, and which are scattered irregularly throughout. Giant cells quite similar to those seen in the tubercles may also be found. In such tissue there are even more definite evidence of the exudation of phagocytic cells from the bloodvessels than in the miliary tubercles themselves. Not only are there great numbers of lymphoid cells, but all those varieties of phagocytic cells which Maximow derives from the outwandered lymphoid cells are to be found in abundance. Particularly striking are the large irregular or rounded cells with large nucleus and very abundant protoplasm which are often most actively phagocytic, being found laden with fragments of cells and nuclear debris of all sorts. Typical plasma cells occur also in great profusion, and indeed it was in such tissue that Unna first recognized and described these cells. Polymorphonuclear leukocytes are not lacking and appear often in the most bizarre and distorted forms. The more superficial parts of the granulation tissue are usually somewhat œdematous and fibrin filaments can be demonstrated throughout. Such tissue, despite its rather rich vascular supply, contains tubercle bacilli and consequently undergoes the same necrotizing process as described for the miliary tubercle. Areas or foci of yellowish opacity appear below the surface of the pale grayish-pink, translucent granulations, and soon become confluent. In the same way the more superficial parts become opaque and yellow, and soon the whole becomes covered with a ragged grayish-yellow, pasty material, which is readily dislodged from the surface, and when the granulations form the lining of a sinus, constitutes, in part at least, the discharge. When formed

upon a surface such as that of the pericardium and pleura the granulation tissue is usually covered with a thick, shaggy, yellow layer of fibrin, and is associated with an abundant exudate of fluid, which may be quite clear, or turbid with floating shreds of fibrin, or at times deeply blood-stained.

While the fresh granulation tissue in an active process shows the characters just described, there are tuberculous processes so slow in their development that there is time for the contraction and induration of the new tissue, and much of it escapes necrosis. The result is a scar-like tissue which may become extremely hard and firm and which may finally reach a considerable bulk. When this appears over the surface of the lungs or heart in the form of adhesions, binding the opposing surfaces together, it may by its rigidity and continued contraction cause great disturbances in the function of those organs. In the substance of organs such as the lung it may produce the densest and most widespread induration. The presence of such tissue in quantity is of course an indication of the very slow progression of the disease. Microscopically it is found to consist of an extremely compact fibrous tissue, in which no indication of its tuberculous nature may be found over large areas. Foci of plasma cells and lymphoid cells with scattered granules of blood pigment may occur. In other places, however, patches of caseation and groups of epithelioid cells or occasional giant cells may give indication as to its nature.

Other types of tuberculosis occur in which the lesion is for a time at least exclusively exudative in nature, *i. e.*, an acute inflammation. These are the instances in which the introduction of quantities of virulent bacilli into the tissues of a person of feeble resistance results in a destructive lesion which advances with extraordinary rapidity. Acute tuberculous inflammations are seen in their purest form in the lungs, but occur also in other places, such as the serous cavities and the meninges. The invasion of the bacilli, for example, into the lungs seems to produce an injury so intense that it is responded to by a sudden pouring out of the elements of the blood almost exactly as in the case of the ordinary lobar or lobular pneumonia. The alveolar epithelial cells are desquamated and fall into the air cells, together with the abundant leukocytes and red corpuscles, which with the fibrin network and exuded fluid soon form a solid exudate very much like that in the simpler types of pneumonia. Characteristic of this sort of acute inflammation is its inevitable fate, which is necrosis or caseation involving not only the exudate but the included tissue. If the patient lives even a short time after the completion of this process, further proof of its tuberculous nature is given by the development of ordinary tubercles and tuberculous granulation tissue about the caseous area, and if life be further continued the picture may come to resemble closely or precisely that produced in the other ways described.

The intimate relation which exists between these forms of tuberculous lesion may be readily seen. Since the demonstration of the tubercle bacillus by Koch there can be no further question as to the unity of the process. It is plain that although bacteria which are secondary invaders

may occasionally appear, the tubercle bacillus is the essential cause of all the changes. Further, even on anatomical grounds there is no very sharp line which we can draw between them. The acute inflammatory form involves the most rapid reaction on the part of the vessels and wandering cells, and it is only in the later stages that proliferative processes occur, although finally they also appear. In the miliary tubercles, as Wechsberg has shown, we have also a primary injury, a response on the part of the leukocytes, which, however, is soon masked by the excessive reaction among the fixed cells. The fact, however, that if sufficient time elapses there are almost invariably traces of the formation of tubercles and the analogous tuberculous granulation tissue in the margins of the areas of acute inflammation shows clearly enough that these are varieties of the same process. The difference in the anatomical result seem to be due to a number of circumstances, among which perhaps the specific power of resistance of the individual is most important. In most persons the bacilli meet with unfavorable conditions for growth, so that they are almost at once destroyed by the phagocytic cells or at most produce only a small local lesion which is soon completely encapsulated and healed. In others, however, they spread like fire in flax, destroying the tissues with frightful rapidity. Further, the virulence of the particular organisms introduced and their number are of great importance in determining the type of lesions, for while small numbers of bacilli inhaled into the respiratory tract may be fairly well restrained in their growth for a time, they may multiply slowly in the tissue, gradually gaining power to overcome the destructive influence of the protective agents of the body. Such a focus of "acclimated" tubercle bacilli may appear, for example, as a caseous area in a bronchial lymph gland; then if the adjacent bronchial wall be eroded through by the advancing necrosis, great quantities of highly virulent bacilli are suddenly discharged into the bronchus and further into the lung, usually causing the so-called *phthisis florida* or *galloping consumption*. In this case, although the changes in the bronchial lymph gland are found to consist of conglomerated and caseous tubercles, those in the lung have the type of an acute exudative inflammation.

The spread of the tuberculous process and the consequent destruction of tissue are limited in greater or less degree by the erection of a resistant barrier of scar tissue by the surrounding structures, which may in time accomplish the complete healing or cicatrization of the lesion. In fact, one may discover, in nearly every autopsy upon the body of persons in advanced life, the pigmented scars of such healed tuberculous lesions.

In addition to the actual destruction of tissue, certain general results of the existence of tuberculosis in the body become apparent. Great emaciation of the whole body usually accompanies the disease, although in exceptional cases extreme obesity persists. In the later stages the emaciation is associated with a peculiar cachexia which is very characteristic. With this, anemia of a secondary type may become extreme. In the internal organs the effect of the toxins is often to cause epithelial degenerations, so that it is not uncommon to find profound fatty metamorphosis of the liver and kidneys, doubtless partly due also to the

anemia. Indeed, one sometimes finds the liver weighing far more than normal and loaded with fat in a tuberculous case in which the emaciation has proceeded to the greatest extreme.

Modes of Entry and Distribution of the Bacilli.—The conditions of existence of the tubercle bacilli outside the body are sufficiently well known to explain fairly well the mode of entrance, although much discussion has arisen as to the relative frequency of these different modes of entry. This subject is treated in the preceding section.

After the admission of the active bacilli into the body there are certain conditions which govern their localization and growth. Of these the mechanical means of distribution are very important, but certain tissues offer more favorable soil for the growth of the organisms than others. Thus, for reasons with which we are not acquainted, the apical portions of the lungs are particularly prone to such lesions. So also are the adrenal glands and the epididymis, while tuberculosis of the lower part of the lungs ordinarily appears only later and secondarily, and tuberculosis of the testicle almost regularly only as a result of tuberculosis of the epididymis. Even more important and interesting are the points of least resistance which may be constituted temporarily by some injury of the tissue or disturbance of its nutrition. Good examples of this are described by surgeons in the development of tuberculosis of bones or joints after their injury by fall or strain.

The mechanical distribution of the bacilli is affected in several ways, depending largely upon their mode of entry. Of these one of the most common is that in which the bacilli are carried along the lymphatic channel until they lodge in the sinuses of the lymph glands which form stations in those channels. In their course many of them adhere to the endothelial walls and there produce tuberculous lesions, and where, as in the case of the mesenteric lymphatics, an opaque lymph is ordinarily carried, the canals become very conspicuous by their distension with chylous fluid, which can only with difficulty pass the obstructing tubercles.

Thus we find the peribronchial lymph glands regularly involved in a tuberculous, caseating process when there is tuberculosis of the lung, the mediastinal and retroperitoneal glands in cases of tuberculous peritonitis, mesenteric glands in intestinal tuberculosis, and so on. The distribution in the lymphatic system is thus seen to correspond closely with that of any foreign particles which get into the tissues or that of the cells of an invading carcinoma. In certain cases even the thoracic duct becomes the seat of mural tuberculous lesions which may cause partial obstruction, but which allow of such extensive sifting of tubercle bacilli into the blood stream as to give rise to a generalized acute miliary tuberculosis.

This last is one common mode of wholesale introduction of bacilli into the blood stream, but another method exists, namely, the rupture of a caseous gland directly into a vein. The wall of the vein becomes involved in the tuberculous process from without, and as caseation advances it slowly eats through the wall until finally a friable plug of yellow material loaded with bacilli projects into the blood stream, or the semifluid

caseous material is actually washed out of the gland into the vein. This, again, is almost always followed by a widespread miliary tuberculosis.

Similarly, the great serous cavities may become infected by the rupture into them of adjacent caseous lymph glands or by direct extension from a tuberculous lesion immediately underlying the wall of such a cavity, as, for example, a tuberculous ulcer of the intestine. Direct extension of the lesion is perhaps better exemplified in the so-called ascending genito-urinary tuberculosis in which, one after another, epididymis, vas deferens, seminal vesicles, prostate, bladder, ureters, and pelvis of the kidney are affected, although whether the extension occurs in this order or not has been the subject of recent discussion.

In a very similar way tubercle bacilli may be transported from one part of the intestinal tract to another, giving rise to ulcerative lesions as they go, and from one part of the lung to another along the bronchi by the aid of the respiratory currents of air and gravity.

Acute Miliary Tuberculosis.—It is not easy to draw a sharp line between generalized and acute miliary tuberculosis and the occurrence of scattered tubercles of various ages in the organs in association with tuberculous disease of longer standing. The type, however, of acute miliary tuberculosis as generally recognized is that condition in which with high fever and a stuporous intoxication resembling that of typhoid fever there is found at autopsy a general distribution of minute tubercles, all of practically the same age and size throughout almost all of the tissues. In such a case we may presume that the bacilli reached the tissues at about the same time and therefore that they must have been conveyed by the blood stream. The same is true of those tubercles which are scattered in numbers in the organ, but which vary greatly in age and size, except that in that case the bacilli apparently gain access to the blood stream a few at a time, rather than in the sudden wholesale way which may be demonstrated in the typical generalized miliary tuberculosis. In those typical cases it has become more and more evident since Weigert's publications on the subject, that if sufficient search be made an intravascular tubercle directly distributing bacilli into the blood stream or an ulcerative tuberculous lesion of the thoracic duct may be found. The percentage of positive results in the search for vascular tubercles in cases of miliary tuberculosis is very high (70.8 per cent. in Weigert's cases, 82.8 per cent. in Sigg's, and over 90 per cent. in Schmorl's cases).

The tissues contain a very great number of nodules, not billions, however, but thousands, as Cornet points out, and still if one remembers the small size of the bacilli, it will be seen that enough bacilli to produce so many nodules may be easily furnished by a small quantity of caseous material rich in organisms. Tuberculous lesions of the vessels which involve the direct exposure of caseous bacillus-holding material to the blood stream are found most commonly in the pulmonary veins, although they also have been found repeatedly in the vena cava superior and less often in the azygos, adrenal, jugular, and cerebral veins. Careful examination of these lesions shows that they fall into two groups which, as pointed out by Benda in his recent admirable review (Lubarsch and Ostertag's *Ergebnisse*), are the result of different processes. In the one

instance a tuberculous process approaching the vessel from without erodes its outer wall, and may in time perforate it, either causing thrombosis or by its more sudden advance entering the vessel before it has time to be obliterated and discharging the caseous material with bacilli into the passing blood stream. This is the so-called periangeitis caseosa.

On the other hand, the tuberculous lesion may be limited to the intima of the vessel and evidently produced by the deposition of floating tubercle bacilli from the blood stream upon it. Such lesions may occur in the endocardium or in the intima of the aorta or even of the smaller arteries, but are more common in the veins. In a recent case in which such a caseous mass was found in a pulmonary venule, the lumen of the venule was completely filled so that no blood passed and it would have had no significance in the further distribution of bacilli had it not grown to project free into the larger vein into which the branch emptied. From this free end there was sufficient distribution of bacteria to produce tubercles in all the organs

Finally, tuberculosis of the thoracic duct may be the result of the invasion from a neighboring tissue, but apparently more often follows the distribution of bacilli upon its intima or the extension of caseous thrombi of its branches into it. It may affect only one area, or almost the whole length of the duct may be involved, with occlusion here and there and ulceration of the masses which line it. Stasis of lymph and the development of collateral circulation are generally evident. Such a duct will of course pour quantities of bacilli into the circulation.

The sudden development of so much tuberculous tissue throughout the body doubtless gives a ready explanation of the profound symptoms observed in acute miliary tuberculosis. It is true that there may be quite as much destruction of tissue and perhaps as many bacilli in an extensive pulmonary tuberculosis, but in that case the poisons produced are concentrated in the lung and prevented, by the destruction of the bloodvessels there, from being carried to the rest of the organs.

Tuberculosis of the Respiratory System.—Nose.—The mucosa of the nose is probably more often the seat of tuberculous lesions than is generally supposed. It may be infected from soiled handkerchiefs or fingers, from the passage of tuberculous sputum when the lungs are affected, or perhaps by the direct inhalation of tubercle bacilli. Experimentally it has been shown that tuberculosis of the nasal mucosa of guinea-pigs may be produced without any wound of the mucosa by spraying tubercle bacilli into the nostril. Further, it has been shown that in normal individuals tubercle bacilli may sometimes be demonstrated in the nasal secretion. The lesions, according to Herzog and others, may be ulcerative upon an infiltrated base, they may form circumscribed tumors, or they may consist in a combination of these types. They affect most often the vault of the nasal cavity where it passes over into the pharynx, the septum, and the inferior turbinate. The accessory sinuses, however, may be involved and caries of the sphenoid and other adjacent bony structures has been reported. In certain cases, as is true also of the mouth, pharynx, and even of the larynx, the lesions of lupus may extend from the skin into the nasal cavity.

Larynx and Trachea.—Tuberculous disease of the larynx may be primary but is most commonly due to infection from the passage of tuberculous sputum from a cavity in the lung. Tubercles are formed just beneath the epithelium of the mucosa and by their confluence and caseation give rise to ulcers which may be shallow lenticular defects with reddened base and sometimes edged with yellow, or large ragged, irregular and deep ulcerations. The first or aphthous erosions are especially characteristic of the trachea and occur in great numbers. The more extensive ulcerations affect usually the vocal cords, aryepiglottic folds and the epiglottis but may grow to involve most of the larynx. They are very destructive, extending down to the cartilage and denuding it or even excavating it deeply. The erosion of the vocal cords makes phonation impossible and destruction of the epiglottis renders swallowing very difficult. Sometimes in the course of such a destructive ulcerative process a secondary infection may occur, producing a phlegmonous or gangrenous laryngitis, often with a rapidly fatal result.

Lupus-like proliferative forms of tuberculosis occur in the larynx and may be direct extensions from similar lesions in the pharynx. They produce flattened elevations and shallow ulcerations and subsequently extensive scars. Recently, Panzer and others have pointed out that papillary excrescences formerly regarded as papillomatous in nature may in many cases be tuberculous. These are often pedunculated or sessile, cauliflower-like structures which are bluish in color and ragged or uneven superficially, and are largely composed of tubercles and tuberculous granulation tissue. Cases of healing of tuberculous ulceration of the larynx are extremely rare: partial healing may frequently occur and cicatrization be extensive enough to produce stenosis of the larynx.

Bronchi.—Tuberculous lesions of the bronchi are practically invariably associated with tuberculosis of the lungs and may be described with that condition.

Tuberculosis of the Lungs.—The pathological anatomy of tuberculous disease of the lungs presents a remarkably varied picture, the changes differing greatly in character according to the intensity of the affection and the consequent duration of the disease. These variations depend upon the number and virulence of the bacilli and their mode of introduction, and, on the other hand, upon the resistance of the individual.

Under ordinary circumstances the disease begins in the apical portion of the lung, not quite at the apex, but usually at a point about 2 cm. below the extreme apex, and there the primary lesion usually takes the form of a small, caseous focus involving the termination of the small bronchus which extends from that point. Indeed, Birch-Hirschfeld insists that the mode of formation of the initial lesions consists essentially in the primary localization of the inhaled bacilli in the terminal portion of the bronchus just as it passes over into the atrium and in the formation there of a caseous and ulcerative bronchiolitis which soon extends to involve the adjacent air cells and the neighboring bronchial wall. The reasons for the localization of the process in this particular part of the lung are not perfectly clear since other portions are seen to be quite susceptible to the infection. The current explanations on the

basis of the relatively imperfect mobility of the apex, its insufficient aeration and less abundant blood-supply, which render it a favorite soil for the bacilli, are rather unsatisfactory. Freund especially emphasizes the immobility which may result from the pressure of the first rib and Bacmeister has artificially immobilized the apical part of the thorax in rabbits and found that intravenous or other inoculation of bacilli then produces an apical tuberculous lesion. Whether the course of the bronchus leading to the apex favors the entrance of bacilli to that portion is at least questionable.

Probably cicatrization of the apical lesion results in a very great number of individuals in whom tuberculosis has never been recognized and thus permanently cuts short the progress of the disease. Such are the cases in which tight adhesions are found between the pleural layers over the apex of the lung and beneath them a rather thin, flattened scar which extends only a short way into the substance of the lung. In other cases there are no adhesions, but merely a scale-like puckered thickening of the pleura at that point, with much gray and black pigmentation, both in the scar and in the immediately adjacent lung substance. There seems room for doubt as to the exact nature of such scars, although they are generally regarded without question as tuberculous. They are extremely superficial and involve the destruction of very little of the lung substance and not that portion (subapical) which is usually seen to be affected in the primary tuberculous lesions. Further, they frequently show microscopically no evidence of caseation nor anything resembling a tuberculous tissue, nor can bacilli be demonstrated in them. They consist merely of dense fibrous tissue in which remnants of partly obliterated alveoli with thickened epithelium and terminal bronchioles may persist and in which granules of coal-dust and blood pigment are usually abundant. The evidence of their tuberculous nature in such cases is therefore largely presumptive. Much more definitely tuberculous in nature are those scars which extend in pyramidal form much deeper into the tissue, and pucker and distort the apex of the lung. Such masses of hard, dry tissue are also deeply pigmented and sometimes contain calcified areas. The microscope frequently reveals definite remains of tuberculous tissue and encapsulated caseous tubercles in these. Whether such scars offer any menace to the individual depends of course on the completeness of the encapsulation of the bacilli, but in general they are probably to be regarded as finished.

When the conditions are more favorable for the growth of the bacilli the apical lesions may extend with varying degrees of rapidity to the other parts of the lung. Usually the extension is at first quite local and leads merely to the enlargement of the focus with the involvement of the surrounding pulmonary tissue. With the advance of the necrosis the bloodvessels become completely obliterated so that when the caseous material is finally liquefied and discharged into the central bronchus, whose walls were the first to be destroyed, no hemorrhage takes place. In such early lesions the discharge of the caseous matter into the bronchus is practically always possible on account of the inevitable wide connection of the bronchus with the cavity or vomica thus formed, and one can at

autopsy almost invariably pass a probe from any tuberculous cavity directly into a bronchus. The cavity may be no larger than a marble, but the emptying of its contents into a bronchus is usually the first step in the wide involvement of the lung in the tuberculous process. The presence of the material, loaded as it is with tubercle bacilli, in the larger bronchi provokes violent respiratory movements and cough, and these aided by gravity soon effect the distribution of the bacilli back into the previously uninfected bronchi.

When the aspirated substance reaches the finest bronchioles and the associated air-containing tissue, tuberculous lesions quickly result, and these again vary somewhat in character according to the virulence and number of the bacilli and the consequent rapidity and extent of the change. Apparently they are ordinarily of pneumonic or exudative character in the earliest stages, but when they come to view at autopsy they have usually had time to undergo a partial caseation, together with the marginal development of irregular conglomerated tubercles which add to the firmness of each patch and render them indistinguishable from partly caseous conglomerated tubercles, except by the fact that the microscope reveals the framework of the air cells, which is outlined throughout the caseous area by the elastic tissue, undisturbed in its relations. This seems characteristic of a pneumonic area, for the primary development of conglomerated tubercles in the air-containing tissue leads to the displacement of the walls of the air cells and their great distortion before they have time to undergo caseation. Nevertheless, it is by no means uncommon in such cases to find abundant miliary and conglomerate tubercles scattered throughout the lung as the result of the aspiration of infected material. If the anatomical study of the lung can be carried out soon enough after the aspiration of the bacilli it is easy to distinguish microscopically between the minute areas of pneumonia and any definite fresh tubercles which may occur. Still, as described, the exudative processes, the proliferative process, and the process of necrosis are so quickly combined that in principle a fairly uniform result ensues. The gross appearance of such a lung may, however, vary greatly. It is most common on section to find the lung moist, but not particularly hyperemic and studded throughout with firm patches of various sizes which are usually ranged around the bronchi like clusters of grapes about the stem. These consolidated patches, when very small, may be pearly gray and semitranslucent, and most easily recognized by the palpating finger; but when large they present a flat surface elevated a little above the cut surface of the lung and roughened and opaque or dull in appearance. In color, they alter with age from a grayish red, through gray to a pale yellowish white. With the further lapse of time they undergo softening and liquefaction and a greenish hue may become apparent in the caseous material. In other instances the patches are much firmer and project mulberry-like above the cut surface, giving it a very nodular appearance. The lung tissue about the more acutely formed patches is often translucent and exudes on pressure a tenacious glutinous fluid.

No fundamental distinction can be made between this type of

pulmonary disease and that which was so clearly described by Fränkel and Troje under the name of *acute pneumonic phthisis*. In that condition the sudden introduction of large numbers of virulent tubercle bacilli into the bronchi results in the rapid appearance of a widespread consolidation of a whole lobe or even of the whole lung, so that the condition is often regarded as ordinary acute lobar pneumonia. In no essential point, except in degree of involvement and rapidity of development, does this alteration differ from that just described in the acute lobular bronchopneumonia. The appearance of the lung is, however, very characteristic, especially in the more advanced stages. At first the consolidated area has practically the appearance of that seen in acute lobar pneumonia. The whole lobe is evenly consolidated, its pleural surface being dulled by an opaque deposit of fibrin. The cut surface is roughened by minute fibrinous plugs, and the whole opaque, dull-looking area has a grayish or grayish-red color. The adjacent lung not actually involved in the definite consolidation has the gelatinous semitranslucent appearance described also for the lobular pneumonia, and if one strokes it with a knife it is sometimes possible to draw up into strings the gelatinous fluid which exudes from it. It is rare, however, that the lung in this condition shows only these appearances; ordinarily some part or all of the consolidated area has undergone the inevitable caseation or coagulative necrosis so characteristic of tuberculous lesions. Usually, this is irregularly distributed so that the cut surface has a marbled appearance, but sometimes the whole lung is quite uniformly converted into a homogeneous, yellowish-white material which cuts smoothly like cream cheese and shows no living tissue with the exception of the largest vessels and bronchi. In such cases the small cavity in the apical portion of the lung may show clearly the mode of distribution of the infectious agent. If an attempt be made to inject such tuberculous lungs, it is found that the injection mass stops short at the margins of the necrotic areas, although the capillaries are still quite patent in the gelatinous area and in the fresher portions of the pneumonic consolidation. In such a case in which the whole substance of the lung had undergone caseation, the colored mass would enter only the larger vessels.

Microscopically, the development of these lesions is about as follows: Under certain circumstances the bacilli may spread along the lymphatics or for a short distance through the tissue and set up the formation of miliary and conglomerated tubercles of the usual type. As will be described, such tubercles may develop throughout the lung when the bacilli enter by the blood-stream.

As to the earliest stages in the formation of the pneumonic lesions we are able to judge chiefly from the appearances of the changes in the neighborhood of the more advanced lesions. There we find bloodvessels distended with blood and the air cells filled no longer with air, but with a fluid the viscidity of which is indicated by the deep eosin stain which it takes in the section. Many large cells with round vesicular nuclei and abundant protoplasm, often studded with fat globules, lie in this fluid, and are for the most part to be regarded as the desquamated alveolar epithelium from the walls of the air cells.

Mononuclear leukocytes of various sizes, a few red corpuscles, and increasingly abundant polymorphonuclear leukocytes are soon associated with these. A dense network of fibrin is not long in forming, and finally, except for the great abundance of desquamated epithelial cells, the appearance is not unlike that of ordinary pneumonia.

Scarcely, however, is the exudate completely formed when the change occurs which is particularly characteristic and which will serve at once to distinguish tuberculous pneumonia from the ordinary forms. This is the process of coagulative necrosis which changes the cellular exudate into the red staining formless material, in which at first abundant deeply staining fragments of nuclei are visible. They are seen as fine dust-like particles in clouds about the margin of the caseous area, where they are conspicuous by their deep blue stain. Elsewhere the whole area is converted into a fairly homogeneous refractile granular pink or red staining substance. In time the caseous material becomes more and more homogeneous, although at first shadowy outlines of the cells of the exudate are distinguishable. The walls of the air cells which are also involved in the necrosis fade away gradually and are finally lost in the softening debris. As long, however, as the caseous material retains its firm consistency these walls can be distinguished usually as faint lines of pale blue. By the aid of Weigert's special stain for elastic tissue they may be plainly brought to view as a network of deeply staining fibrils, for it is chiefly owing to the great abundance and great powers of resistance of the elastic tissue that they remain visible so long. Even after the caseous area becomes liquefied and is expectorated through the bronchi, shreds of elastic tissue persist and may be recognized in the sputum. The presence of the elastic tissue, in the normal architectural arrangement without distortion, throughout the caseous area, gives proof, as mentioned, of the pneumonic origin of the lesion rather than its dependence upon the formation and subsequent caseation of tubercles. Certain other structures persist within the caseous areas and may remain recognizable for a long time. Particularly resistant are the larger bloodvessels the walls of which become extraordinarily thickened on the stimulus of the advancing destructive process. The thickening is especially seen in the inner layers, which become so increased in bulk as to obliterate the lumen of the vessel—the so-called obliterative endarteritis. Coal pigment in the walls of these vessels is an aid in their recognition. The bronchi which are included are also often distinguishable by the presence of coal pigment in their walls, but they show far less power of resistance than the bloodvessels. Indeed, their walls are quite commonly involved in the caseous process throughout considerable lengths.

In some instances the bronchi are rendered conspicuous by the great thickening and subsequent caseation of their walls, even when they are not completely surrounded by caseous material, so that they run as thick-walled tubes of opaque, yellow material through the gelatinous or partly consolidated lung.

Even when the caseation is apparently quite homogeneous over an area of the lung, it is often seen on microscopic examination that there

are in the firmer caseous substance rounded and irregular cavities which contain a loose network of coarse fibrin filaments, often with scarcely any cellular remains. These are often at the terminations of the small bronchioles, where they pass over into the vestibule and atria; in many cases they are surrounded by the remains of the walls of normally disposed air cells and have not been produced by the breaking of one air cell into another. The most plausible explanation of their presence seems to be that the solid caseous material once formed may be in small part discharged through the bronchus or it may contract in such a way as to leave cavities such as are seen in a Swiss cheese. The coagulation of new fluid which permeates into these cavities results in the coarse, loose networks of fibrin described.

Up to this point, then, we have larger or smaller areas of pneumonic consolidation in which the greater portion is completely necrotic, although still showing indistinctly the architecture of the tissue, while the marginal portion, although still living, is densely infiltrated with the cells of the exudate fluid and fibrin. Such areas are surrounded by wide halos of the gelatinous infiltration in which the air cells are filled with fluid and desquamated epithelial cells. This is the so-called *caseous* and *gelatinous pneumonia*.

The further outcome of this condition varies considerably. Actual resolution is probably unusual if not entirely impossible when the consolidation is completed. In the areas of collateral œdema or gelatinous pneumonia which surround the patches of consolidation it seems probable that the exudate may disappear in case the actually caseated area becomes limited and encapsulated. This must be chiefly a mechanical process, for any such general autolysis and dissolution of the exudate as occurs in lobar pneumonia of the ordinary type seems to take place only in the slightest degree, if at all, in tuberculosis. Further, the obliteration of the bloodvessels, which is practically never observed in the ordinary pneumonia, takes place very early in the tuberculous process, and that area is then completely cut off from any hope of favorable influence from without.

When the caseation is complete it is usually found, in those cases in which the patient has lived at least a short time after the death of the tissue that organization of the exudate which has not become necrotic occurs. This accordingly affects the contents of the alveoli around the margins of the caseous area and is in every way analogous to that sometimes seen in ordinary pneumonia, in the margins of the necrotizing areas in glanders of the lung, in actinomycosis, etc. Ordinarily the organization as it appears a little distance from the caseous area is non-specific in character and not to be distinguished from that seen in any bronchopneumonia. Within this, however, and immediately adjacent to the caseous area, abortive irregular tubercles and dense tuberculous granulation tissue develop in which giant cells are frequent and epithelioid cells form the predominate element. These processes together form a fairly dense fibrous wall about the caseous mass, a wall which is, however, prone to further necrosis and disintegration. The walls of the air cells and vessels, which in this type of pneumonia become

especially intensely infiltrated with the cellular exudate, are included and built up into this capsule.

Sometimes such an encapsulation is effective in limiting the further action of the tubercle bacilli upon the tissues, the caseous material is retained by it and becomes denser and dryer, until finally with the deposition of calcium salts it may practically be converted into a stony or mortar-like substance. Usually, however, a quite different result ensues. The caseous material becomes softened and finally liquefied or broken down into a mushy, thick fluid which is discharged into the open bronchus and when mingled with the mucous secretion of the bronchus forms the green sputum which, according to Fränkel and Troje, is so characteristic of the acute caseous pneumonia.

The discharge of this material leaves a cavity which, when all the caseated tissue is liquefied and expectorated, corresponds in form and size with the focus of pneumonia. In some cases, in which the caseation advances with great rapidity and quickly involves large areas of the lung, the cavity formation may also be extremely rapid and extensive so as to practically completely destroy the lung within a very short time—the so-called *phthisis florida*. The wall of such a cavity consists of a more or less dense membrane-like layer of tissue, the lining of which is composed of necrotic, shreddy material which remains after the discharge of most of the caseous area. Beneath this is the tuberculous granulation tissue which is essentially the same, no matter where formed. Even outside of this in the earlier stages there is the lung tissue partly consolidated by cellular exudate, partly by loose plugs of fibrous tissue which lie in the air cells. There is a constant attempt at the production of a firmer wall by the proliferation of fibrous tissue cells, but when the bacteria are very virulent and abundant and the resistance of the individual slight, as in the case of *phthisis florida*, continued extension of the cavity may occur. Such a cavity usually contains a considerable quantity of residual fluid and caseous material in which a great variety of bacteria and occasionally even moulds and fungi may be demonstrated. This abundant flora has been extensively studied by Stephen Artault and others,[1] and there has arisen some question as to the part played by the tubercle bacillus in the production of the lesions. The weight of evidence is in favor of the idea that the whole process, as far as complete caseation, may be and is produced by the tubercle bacilli alone. The liquefaction of the caseous material may, however, result from a secondary infection, and it is apparently quite true that many of the symptoms —fever, general evidences of intoxication, etc.—which arise in the late stages after the cavity has become further infected, are largely dependent upon the presence and growth there of other organisms.

The walls of the cavity are, as a rule, not smooth, but roughened by the irregularities of the necrotic substance. Further, there are usually prominent ridges or sometimes cord-like structures, stretching across, which on section are found to be bloodvessels whose walls are greatly thickened and very firm. They are on this account so resistant as to

[1] *Arch. de Parasitologie*, 1898, tome i.

remain after the tissue around about them has been destroyed and removed, and they are quite isolated. Frequently they are entirely obliterated and on section are seen to be merely solid cords of fibrous tissue. Sometimes they are eroded through and the ends hang free in the cavity. This type of obliterating endarteritis is obviously a protective process, preventing hemorrhage from even the larger vessels, which would otherwise be rapidly opened by the ulcerative process. Occasionally, the advance of the destructive process is more rapid than the obliterative change in the vessels and a severe hemorrhage may be the result. The bronchi usually stop abruptly as they enter the cavity, their walls having been destroyed. They may be somewhat dilated, but, as a rule, especially in the rapidly destructive cases, the changes which are evident in those portions of the bronchi which remain consist chiefly in the ulceration of their walls; the shallow ulcers pass into the mucosa and submucosa and leave a rough, raw surface within the bronchi.

The cavity, which is most commonly in the upper lobe of the lung, although by no means always so, may involve practically the whole lobe, or by extension nearly the whole lung. Such large cavities are always associated with abundant tubercles and areas of tuberculous pneumonia in the remainder of the lung. Often the lung is reduced to a mere sac, of which the thickened pleura forms practically the only wall, all the lung substance having been destroyed. Occasionally, if the pleural cavity has not been obliterated by adhesions, a perforation may take place through this thin wall, with the escape of fluid and *air* into the pleura. In every instance of such extensive cavity formation there is tuberculous pleurisy, but in such a case the admixture of air and abundant foreign bacteria and necrotic material sets up a *pyopneumothorax*.

Death is not necessarily the immediate result when such destructive processes occur in the lung. Indeed, the tendency toward healing, which is recognized in the attempt at encapsulation of the lesions, is often given play by the continued life of the individual, so that extensive scar formation takes place and the consistency and appearance of the lung may be greatly altered.

It has been mentioned that in tuberculous pneumonia, etc., the substance of the lung tissue, the walls of vessels and bronchi, and the septa between the air cells become much infiltrated with cellular exudate. Perhaps in consequence of this intimate affection of the tissue the fibrous tissue is stirred up to proliferation and the walls of the air cells become thickened. Such general thickening of the tissues, which in course of time become very firm and scar-like, is often spoken of as indurative or interstitial pneumonia, and although it is found in connection with other infections is perhaps most commonly seen in tuberculosis.

In certain instances the walls of the air cells become so thick and rigid that they are no longer capable of distension, and the lining epithelium wherever it is preserved returns to its embryonic high cubical form so that the air cells come to look almost like the acini of a gland. Sometimes, indeed, they are widely separated by thick bands of fibrous tissue. Such an indurated lung is firm and elastic and has a grayish-black color.

In the cases where the power of resistance of the individual is sufficient to allow of such a scar formation, the caseous areas and cavities usually become well walled off, and it is self-evident that in such individuals the cavities and caseous areas could hardly reach the maximum extent. Actual healing may be accomplished or the tuberculous areas are at least so far encapsulated as to be rendered practically harmless. The same thing may, under exceptional conditions, occur in the case of cavities of considerable size, which then become cleaned out, and all the necrotic material expectorated, leaving a smooth, firm, fibrous wall, over which epithelium grows from the bronchus. This, however, must be regarded as unusual.

All possible combinations of destruction and induration or protective changes may be observed in the lungs in pulmonary tuberculosis, the predominance of one or other condition at autopsy indicating with fair certainty the degree of rapidity with which the disease progressed as well as the power of resistance of the individual and the virulence of the bacteria. It may be repeated, however, that the commonest picture in any great series of cases is that in which at the apex or in the subapical region there is a cavity in open communication with a bronchus and demarcated from the adjacent lung by a layer of tuberculous granulation tissue, while in the lower portions of the lung there are areas of varying size usually ranged in clusters around the bronchi, in which the lung substance is consolidated, and in part, at least, caseous. These may be purely pneumonic in character, in the freshest cases, or in others they may be indistinguishable from conglomerate tubercles, but in most instances they are recognizable as caseous pneumonic areas in the margins of which tubercles and tuberculous granulation tissue have developed. It is, however, to be emphasized that tuberculosis of the lungs is in most cases a chronic affection of some duration, and that, therefore, the indurative changes are generally present.

Tuberculosis of the Pleura.—Pleurisy accompanies all active tuberculosis of the lungs when the lesion approaches the surface but it may also result from extension from an adjacent caseous lymph gland. Whether a tuberculous pleurisy may arise in the complete absence of tuberculous lesions in the adjacent tissues seems very questionable.

Anatomically, the tubercle bacillus may produce directly or indirectly a great variety of lesions in the pleura and all transitions may be observed between the dry, fibrinous form, in which without the presence of any fluid exudate the pleura had lost its gloss, and the most advanced tuberculous empyema. Recent writers tend more and more to look upon pleurisy which begins without apparent cause and without definite pulmonary lesions as tuberculous in origin. These are the so-called idiopathic pleurisies, but careful search will usually reveal some associated lesion generally of tuberculous character, or with the lapse of time widespread and definite tuberculosis may appear. Peron has shown by bacteriological studies the predominant tuberculous nature of such pleurisies, and Aschoff, by inoculation of the exudate into guinea-pigs, was able to produce tuberculosis in the animal as often as by the inoculation of material from definite tuberculous pleurisy.

The lesions in tuberculous pleurisy are entirely comparable to those found in the pericardium and in the peritoneum so that they need not be described separately except to emphasize the frequency with which enormous fibrous thickening of the subpleural tissues occurs in long-standing cases. Complication with secondary infections takes place chiefly when pneumothorax appears.

Particularly puzzling are those cases which occur so frequently at the onset of the illness in which as yet no definite tuberculosis of the lungs or other organs is evident. In these there may be an exudation of clear fluid in which tubercle bacilli are demonstrable only with difficulty. In other cases the fluid has a distinctly hemorrhagic character.

Tuberculosis of the Lymphatic Tissues.—The Tonsil.—Much has been written of late upon the relation of the tonsil to tuberculosis, especially with regard to its importance as a portal of entry, but even after the study of hundreds of cases there is no great unanimity of opinion. That the tonsils become infected by the tubercle bacillus is undoubtedly true, commonly in connection with pulmonary tuberculosis, but sometimes primarily. Most important are the cases of latent or inconspicuous tuberculosis of the tonsil, in which merely an hypertrophy of the tonsil or even no change at all is present. Such infections may take place from the air, sputum, or food, and may give rise to tuberculosis of the cervical and mediastinal glands, and thus to a generalized tuberculosis. Grober, in studying the dissemination of bacilli from the tonsil, concludes that it is quite possible that tuberculosis of the apical vault of the pleura may be due to direct transportation of the bacilli from the tonsils, and suggests that the apical lesions of the lung may arise in the same way.[1]

Tuberculosis of the Lymph Glands.—When definite anatomical tuberculosis of the glands is demonstrated there can be no dispute as to the nature of the condition, but a series of cases appears to exist in which definite proof of the tuberculous nature of the swelling of the glands is not brought forward, but in which there is still the general impression that the whole condition is of a tuberculous nature. Such cases are classed roughly under the name of *scrophula* or *scrofula*, a name formerly much more used than at present, which has fallen somewhat into disrepute. This condition, which occurs chiefly in children and young persons, is characterized (Czerny, Blos, Neumann, and others) by general pallor, hyperplasia of the lymphoid tissue, especially about the throat, susceptibility to infections, and certain other special phenomena, such as circular caries of the teeth, phlyctenular conjunctivitis, and especially the seborrheic eczema of the cheeks and the infantile prurigo (a nodular eruption which itches intensely and tends to suppurate).

The clearly tuberculous lesions may well attract more attention. In general the glands become infected by the absorption of tubercle bacilli from a tuberculous lesion in tissues drained by their afferent lymph trunk, or by the transportation of tubercle bacilli as inert dust-like bodies along this afferent track until they are entangled in the lymph sinuses or in the lymph nodules of the node. In some cases the glands

[1] *Klin. Jahrb.*, 1905, Band xiv.

become greatly swollen and firm, and on section show a surface mottled with yellow patches or uniformly yellow, opaque, and dry throughout. The cut surface is perfectly smooth and the substance is friable and crumbly. They frequently soften into a fluid consistence and the surrounding tissues may be affected by this process, a widespread inflammation of the capsule and adjacent tissue being set up.

On the other hand, another condition occurs in which the glands become swollen and fairly firm. On section they are grayish and rather succulent, and are studded with gray, translucent nodules which, however, may later become conglomerate and undergo caseation and softening, as in the previous case.

The two appearances are fundamentally identical. In the first instance the introduction of the bacilli in numbers causes a diffuse injury and a diffuse exudation of phagocytic cells with proliferation of the epithelioid connective-tissue cells. With the appearance of caseation the tissue at the margin of the caseated area always shows the abortive tubercles, which are also to be found about the areas of caseation in the acute penumonic phthisis. In the second case the scattered groups of bacilli react upon the adjacent tissue in the ordinary way to produce tubercles. Tuberculosis of the lymph glands with caseation is particularly common in the neck, and especially in negroes in this latitude. The channels of infection have already been discussed and the portal of entry may exist anywhere in the upper respiratory tract or in the mouth, the masses of lymphoid tissue situated there probably acting as the direct transmitters of the bacilli. The glands become much enlarged and firm, so that great packets of them may stand out on each side of the neck below the angle of the jaw. In many cases the caseation and liquefaction may end in rupture into the intermuscular tissues, and the discharged material then burrows its way until often the skin is uplifted and finally broken through. A fistulous opening reaching down to the old packet of glands is the result of this discharge, and this becomes lined with thick, tuberculous granulation tissue, which shows little tendency to healing.

In connection with tuberculosis of the glands of the neck, involvement of the axillary and mediastinal glands is not uncommon. In the inguinal region groups of enlarged and caseous glands may occur secondary as a rule to tuberculous lesions of the genitalia, although in several instances tuberculous cutaneous alterations in the foot and ankle seem to be the origin.

The glands most commonly tuberculous are doubtless those situated at the hilum of the lung about the bronchi. These receive the materials absorbed by the lymphatics of the lung, and with them often tubercle bacilli. They, like the glands of the mesentery, may thus receive tubercle bacilli when the general health of the patient is good, and perhaps this may account for the fact that they especially frequently contain completely encapsulated or fibroid tubercles, or sometimes calcified nodules, which represent obsolete tuberculous lesions. With the advance of the caseous process in these glands, bronchi or bloodvessels may be eroded and the bacilli emptied into them, with results recorded above. Tuberculosis of the mesenteric and retroperitoneal and other abdominal

lymph glands is largely a consequence of tuberculosis of the digestive tract or at least of the absorption of bacilli from the intestinal tract, for it must be repeatedly emphasized that the bacilli are not always ready to destroy the tissue, but may behave, in their passage through such tissue as the intestinal wall, as inert particles and leave no trace of their passage. In children it is not uncommon to find the glands in the mesentery swollen into tumor-like masses which on section are found to contain a soft, cheesy material. This is the so-called *tabes mesenterica*, in which there is usually an associated widespread tuberculosis if the child lives long enough, but in which the abdominal tuberculosis is undoubtedly the oldest lesion. Occasionally in adults this form of tuberculosis may occur with really enormous, firm, often calcified mesenteric glands, and sometimes with packets of indurated glands along the aorta. In horses and sometimes in cattle the same condition occurs.

Tuberculosis of the *lymphatic channels* themselves is rarely observed except in the thoracic duct and the intestinal and mesenteric lymphatic vessels, probably because sufficient attention is not directed to them. In the walls of the intestine the lymphatic channels which drain the area involved in tuberculous ulceration of the mucosa are usually distended and rendered conspicuous by the development of tubercles in their lining in such a way as to obstruct the flow of chyle.

Tuberculosis of the Circulatory System.—**Pericardium.**—Tuberculosis of the pericardium, while less common than that of the pleura and peritoneum, is by no means an unusual affection. It exhibits a great variety of forms, all of which, however, are in principle much alike. In cases of generalized miliary tuberculosis the pericardium may become studded with miliary tubercles. What is more generally regarded as tuberculous pericarditis, however, is not merely part of a generalized process. The tubercle bacilli gain access to the pericardial cavity most frequently from the adjacent pleura and lung in cases of pleural and pulmonary tuberculosis, but in many other instances they are introduced from adherent caseous lymph glands. In the earliest stages the tuberculous pericarditis may closely simulate a serofibrinous pericarditis of nontuberculous character, so that it is difficult to be sure of its tuberculous nature with the naked eye alone. In other instances hemorrhages may occur and the fluid exudate is blood-stained. In others it is rendered thick and turbid by flakes of fibrin and cellular exudate. Tuberculous granulation tissue is soon associated with the fibrinous exudate and is thickly studded with tubercles. With the advance of time the caseation of this tissue ensues and the caseous material is added to the rest of the exudate. Ordinarily a sufficient accumulation of fluid to keep the pericardial layers well apart is found only in the more rapidly developing cases, and therefore in the more chronic forms the apposed surfaces become adherent at least in places and later firmly bound together by the thick growth of tuberculous granulation tissue, throughout which caseous foci may be observed.

Myocardium.—Tuberculosis of the myocardium is far less common than the analogous disease of the pericardium. It is, however, probably more common than is usually supposed, especially in the form of a diffuse

miliary tuberculosis, which forms part of a generalized miliary tuberculosis. It has probably no clinical significance.

Endocardium.—Tuberculosis of the endocardium occurs either as scattered tubercles in the endocardial lining of the heart or as actual tuberculous vegetations affecting the valves or extending on to the walls of the chambers. The tubercles when miliary in form are usually subendocardial, according to Benda. They appear as minute white spots usually in the conus arteriosus of the right ventricle, and on section show the ordinary typical structure of a miliary tubercle.

Vessels.—Mention was made of the tuberculous affections of the vessels in speaking of the origin of general miliary tuberculosis. Benda has pointed out that at least two distinct types of tuberculous lesion of the vessels may occur: one in which the adjacent caseous tuberculous focus encroaches upon the vessel from without and finally may erode even to the point of discharging caseous material into the lumen of the vessel, and the other in which the bacilli are deposited from the blood-stream upon the intima and there produce a tubercle which becomes covered with a thrombus and may later undergo caseation and softening. Such intimal tubercles are found in the aorta (Blumer, Longcope, etc.) and smaller arteries, as well as in the veins and thoracic duct. An example was recently seen in a pulmonary vein into which the rounded caseous mass projected from a branch which it completely occluded. This caseous mass was in part overgrown by endothelium and fibroblasts, but it was entirely within the internal elastic lamella, there being only a slight newgrowth of epithelioid cells and occasional giant cells outside that membrane. To these two forms Chiari adds a third, produced by the transportation of bacilli into the vasa vasorum. Perivascular tuberculous lesions developed in the lymphatics of the vessel wall are by no means uncommon in the lung in cases of extensive pulmonary tuberculosis.

Probably the most frequent tuberculous affections of the vessels belong to the first group. Extension of the caseating process takes place just as elsewhere, there being always a proliferation of epithelioid cells in advance. In the case of small vessels, and indeed of all vessels when the process advances slowly enough, an obliterative endarteritis arises, which protects the vessel by obliterating its lumen or by thickening the wall in front of the necrotic area. In other cases the wall of the vessel is weakened by the erosion, and the pressure of the blood bulges it out at that point into a sort of small, aneurismal sac. Such are the altered vessels which give rise to extensive pulmonary hemorrhage.

Tuberculosis of the Digestive Tract.—Mouth.—The mouth is not commonly the seat of tuberculous affections, still there have been reported cases in which the lips, gums, edges of the tongue and palate, as well as the fauces, were infiltrated and ulcerated. Tuberculous ulcerations in these situations have the same character as elsewhere; they are irregular in outline, with somewhat indurated or undermined edges, and with uneven base, frequently showing small, caseous nodules. Such ulceration is very rarely primary, but is usually secondary to pulmonary tuberculosis. In connection with caries of the teeth, however, direct infection may occur and even extend to the adjacent alveolar process

of the jaw. As in the case of the nose, pharynx, and tonsil, lupous granulations which have extended from lupous areas on the skin may occur in the mouth.

Œsophagus.—Tuberculosis of the œsophagus is also extremely rare; possibly largely because of the very smooth lining, which gives no foothold to organisms, and partly because of the rapid transit of infectious materials. Infection may, however, occur from food containing bacilli or by swallowing tuberculous sputum, and the result is the production of nodules which ulcerate sometimes quite deeply.

Stomach.—The rarity of tuberculous ulcers of the stomach is attested by Simmonds' figures, in which among 2000 autopsies upon tuberculous patients 8 cases were found. Glaubitt's percentage is higher, as among 2237 such autopsies he found 47 cases of tuberculous ulcers. Various explanations for the relative immunity of the gastric mucosa have been given. The antiseptic action of the gastric juice is apparently regarded as the most important factor, for, although as shown by the common ulcers in the intestine which result from the deglutition of sputum in tuberculosis of the lungs, the bacilli are not killed by the gastric juice, they are still prevented from settling and growing in the mucosa. An injury to the mucosa affords chance for such localization, and any lesion which causes a diminution in the acidity of the gastric juice will set up conditions which greatly favor tuberculous infection.

Several distinct forms of tuberculous affection of the stomach occur. As part of a generalized miliary tuberculosis nodules appear in the gastric wall, doubtless with considerable frequency. Willms has described in detail tuberculosis of the stomach in which the walls were thickly studded with small tubercles. Finally, there are the ulcerations, sometimes single, often multiple, which doubtless arise from the direct deposition of bacilli from swallowed infectious material. The ulcerations are usually rather small, with irregular outline, elevated, somewhat undermined, indurated margin and rough base, sometimes with tubercles.

Intestines.—Tuberculosis of the intestine is both absolutely and relatively of frequent occurrence, the lesions being rarest in the duodenum, and occurring more abundantly as one passes toward the ileocecal valve, where they are only less common than tuberculous lesions of the lungs. In the colon some evidences of tuberculosis are usually found whenever the small intestine is diseased, and sometimes there are ulcerations there when there are none in the ileum.

As to the mode of infection it may be stated that, with the exception of certain cases, especially in children in whom the tubercle bacilli reach the intestine with such food as milk, they are nearly all secondary to tuberculous infection elsewhere in the body and especially in the lungs. When there is a cavity in the lung it is obvious that the swallowing of bacillus-holding sputum will tend to the infection of the intestine.

It is an interesting question as to whether the bacilli may really be transported like inert particles of dust through the intestinal wall without leaving a noticeable trace behind them. Such is apparently the case in the lung, in which the bronchial glands may show the first lesion, although the bacilli are apparently received by the way of the lung.

Von Behring, indeed, makes great use of this possibility in his explanation of tuberculous infection in general in sucklings. In suckling infants he shows that such bacteria as anthrax may reach the circulation and give rise to a general septicemia, although they pass along the intestinal tract of adult animals without being thus absorbed. Reasoning in the same way he believes that in newborn infants tubercle bacilli may be received in the milk, and pass directly through the intestinal wall to some distant tissue, perhaps the mesenteric lymph glands, where, after lying latent for a time, they give rise to a spreading tuberculosis.

It seems probable, however, that most instances of extensive ulceration of the intestine in adults are due to the swallowing of tuberculous sputum from associated disease of the lungs. The bacilli escape death in the gastric juice and lodge on the intestinal mucosa either in the lymph nodules (Orth) or elsewhere. Their destructive effects are produced as elsewhere by the development of a tuberculous inflammation with tubercle nodules and caseation in the mucosa and submucosa. The discharge of the soft caseous substance into the intestine leaves an ulcer the base of which is lined by necrotic material and often studded with tubercles. Such ulcers tend to grow girdle-fashion around the gut and may penetrate into the muscularis or even perforate the whole wall. They are unlike typhoid ulcers in that they are not limited to the Peyer's patches but run transversely and in that their elevated edges are ragged and undermined. A more characteristic distinction is found, however, in the nodular roughness of the base and the existence of the same nodules on the corresponding serous surface and along the lymphatic channels which lead away from the site of the ulcer to the mesentery. Such lymphatics are rendered conspicuous by the stagnation of white chyle and point the way to the mesenteric glands which are so often involved in the tuberculous process.

It seems probable that such a condition could readily occasion the abundant distribution of tubercle bacilli into the thoracic duct, which, even if no lesion of the thoracic duct arose, could go far toward the production of a generalized miliary tuberculosis.

In the lower end of the ileum, where stagnation of the fecal material is favored, the ulcers become very large and confluent, so that often nearly the whole mucosa is destroyed. Even the intervening mucosa in such cases is not unaffected, being usually the seat of a catarrhal inflammation, which in the colon gives rise to the diarrhœa so common in this condition. In the appendix, tuberculous ulcers of the same character may occur and even go on to perforation. In the colon the ulcerations are more commonly irregular and rounded, although in certain cases they assume the girdle form. The healing of such ulcers is usually interrupted, if it begins at all, by the death of the patient, but sometimes the advance of the process ceases and scarring of the ulcer begins.

The extension of tuberculous ulceration through the wall of the intestine commonly gives rise to fecal abscesses in the neighboring tissue, or, if the conditions are favorable, to the extension of the burrowing to another cavity or even to the outer surface of the body. Thus, tuberculous infection of the mucosa of the anal portion of the rectum may

cause in time the formation of a perirectal abscess, which on rupturing at the anus produces a fistula. The great majority of anal fistulæ have been shown to be of a tuberculous nature, the infection arising from bacilli which have been swallowed or which come from secondary ulcers higher up; the localization of these is favored by the excoriations of the mucosa of the sphincter region, which are so common. The canal is usually lined with very abundant tuberculous granulation tissue. Tuberculosis of the *anus* may also appear in the form of lupous granulations which have extended from the adjacent skin surfaces or even as one of the rarer papular tuberculides of the skin.

Salivary Glands. — Tuberculosis of the salivary glands, formerly thought to be extremely rare, has been reported recently in a large number of cases. The parotid is most frequently affected, the submaxillary less often, and up to the present there is no report of a case of tuberculosis of the sublingual gland. Infection may occur (1) by way of the general blood-stream, in which case the salivary glands become the seat of miliary tubercles, just as do the other organs, or may show a more extensive caseating infiltration; (2) infection may occur along the course of the duct from the mouth, especially when favored by the presence of carious teeth; and (3) there may be extension of a caseous process from adjacent tuberculous lesions in lymph glands, bones, etc. The change in the gland in most cases appears either in diffuse form, with caseous infiltration and softening or subsequent scarring, or as a focal lesion forming a caseous, encapsulated nodule.

Pancreas.—The pancreas seems especially resistant to tuberculous infection, and references to tuberculous lesions other than miliary tubercles are hardly to be found. Lefas describes two cases, but thinks that in those, too, the tuberculous process is really an affection of embedded lymph glands. Parenchymatous degeneration and interstitial sclerosis are often observed in cases of widespread tuberculosis.

Liver.—In sharp contrast with the pancreas stands the liver, in which tuberculous lesions are extremely frequent, being estimated by Simmonds as occurring in 82 per cent. of the cases of tuberculosis which he studied. The lesions are, however, seldom extensive, but consist for the most part of extremely minute tubercle nodules, scarcely visible to the naked eye, but which tend to become confluent, so as to form small or miliary, caseous nodules. In the course of their growth they compress and destroy a considerable portion of the liver tissue and surround themselves with scar tissue. If the process lasts a sufficient time a definite cirrhosis of the liver may arise.

Larger or solitary tubercles may rarely occur in the liver, often near the capsule, sometimes in relation with the periportal connective tissue; commoner than these are the so-called gall-duct tubercles, which start near the bile ducts and directly invade their walls, so that there is soon an open communication between the caseous centre of the mass and the bile duct; they assume the appearance of abscesses with green, semifluid contents. It is probable that these tubercles arise from bacilli brought in by the blood-stream and perhaps transmitted back again by the lymphatics in the walls of the bile ducts, and that they develop outside

the bile duct, invading its wall from without. Nevertheless, attempts have been made to show that they arise from the ascending infection of the bile duct by bacilli from the intestine, and that they extend from the epithelial lining of the duct outward.

Gall-bladder.—Tuberculosis of the *gall ducts* and of the *gall-bladder* have been described in association with gallstones, the whole lining of the gall-bladder having been caseous in one instance.

Tuberculosis of the Peritoneum.—Various types of tuberculous peritonitis occur, conditioned apparently by the virulence and number of the bacilli and by their mode of entry, for while the less virulent seem to produce miliary tubercles and a great outpouring of fluid, the more virulent set up a rapidly destructive caseating process, with exudation of fibrin and many cells. The portal of entry for the organisms may be the blood-stream or the intestinal wall in cases of tuberculosis of the intestine, or the Fallopian tubes in cases of genital tuberculosis or any caseous focus which may extend to the peritoneum. In all of these instances it is therefore secondary to some other lesion, but it seems to have been fairly shown that in some cases it may be the only tuberculous lesion found, and it must be supposed that the bacilli are brought to the peritoneum without causing any extensive lesion elsewhere.

Anatomically, we may find minute miliary tubercles upon the peritoneal surfaces and hidden in the folds of the omentum without any remarkable accumulation of fluid or exudation of fibrin. The peritoneum over them looks quite smooth. In other cases there is a thin exudate of fibrin about them and a quantity of clear or slightly turbid fluid is present in the cavity, sometimes a great quantity sufficient to float up the intestines, which are then quite separate and free. In still other cases a rather vascular, grayish, translucent, tuberculous granulation tissue, thickly studded with tubercles and giving rise to friable adhesions between the intestinal coils, appears on the peritoneal surfaces. These adhesions are most marked when there is no accumulation of fluid in the peritoneum, and indeed they may become quite universal and bind the whole contents of the peritoneum into a dense mass which can hardly be disentangled without tearing the intestines. The omentum in such a case becomes tightly rolled and folded upon itself, so as to assume the form of a firm, solid mass of tissue, which stretches across the abdomen with the transverse colon. In course of time the tuberculous adhesions become the seat of extensive caseation, and it is not uncommon to find secondarily formed spaces and canals burrowing between the coils of intestine in these adhesions. Frequently, such a matted condition of the peritoneal organs is the result of discharge of tubercle bacilli from the outer surface of intestinal ulcers, and the perforation of such ulcers into the adhesions may give rise to fecal abscesses between the loops of intestines or to abnormal communications between adjacent loops.

Localized tuberculosis of the peritoneum is not uncommon, the bacilli apparently affecting the parts of the peritoneum, into which they can sink and rest quietly, such, for example, as the pouches of the pelvis and hernial sacs, which are very often tuberculous. On the other hand, the course of particles in the intact peritoneal cavity is predominantly

toward the diaphragm and hence it is common to find tubercles developing in great numbers on the under surface of the diaphragm.

Healing may occur, especially after operative interference, when the tubercles become gradually smaller and converted into a dense fibrous mass, apparently with the death of the bacilli. Whether the dryer types of peritoneal tuberculosis with extensive adhesions and caseation can heal is doubtful. It is in the cases with well-marked ascites that the best results have been obtained from operation. Every possible suggestion has been made in explanation of this fact, such as stimulus of the operation, exposure to air, production of venous stasis, relaxation of the tissue and improved circulation, exudation of antibacterial serum after the operation, etc. What seems the most plausible explanation is put forward by A. E. Wright, who finds that the fluid in these cases is poor in opsonic power as compared with the blood plasma of that patient, *i. e.*, it has little power to aid the phagocytes to engulf the tubercle bacilli. On its removal, however, new fluid, the blood plasma itself, enters the peritoneum, and by its high opsonic power greatly favors phagocytosis.

Healed types of peritonitis are sometimes observed, as in the instances in which the peritoneum over the liver, spleen, etc., is greatly thickened, even to the extent of contracting and compressing the underlying organ. This in association with similar changes in the pericardium and pleura is usually regarded as tuberculous, but perhaps not upon very conclusive evidence. Healed caseous nodules hanging by long hollow stalks from the peritoneum were described by the writer.[1]

Genito-urinary Tuberculosis.—Kidneys.—Tuberculosis of the kidney may assume widely different forms according to the mode of introduction of the bacilli. In association with tuberculosis of other organs in which there has been some dissemination of the tubercle bacilli by the blood stream, it is not at all uncommon to find small tubercles scattered throughout the cortex or in the pyramidal portion. These may be very small and translucent, but more frequently they are conglomerated into masses which stretch in lines between the tubules and vertically to the surface of the kidney, and are soon caseous and opaque in the central part. This type of renal tuberculosis is of relatively slight importance, since it is usually associated with much more serious and destructive tuberculous lesions in other organs.

There is another type of tuberculosis of the kidney usually associated with tuberculous lesions of the rest of the genito-urinary organs, but not necessarily with any general or disseminated tuberculosis. This is a localized process often affecting only one kidney. Israel describes it as beginning in the substance of the organ between cortex and pyramid and extending downward, while in other cases it begins as an ulcerative process in the points of the papillæ or in the angles of the calices. To explain the first of the types Aschoff speaks of the development of tubercles in the conducting tubules from bacilli arrested there in the course of excretion. Caseation of such conglomerated tubercles produces a cavity which finally opens into the pelvis and extends by a new formation

[1] *Johns Hopkins Hospital Bulletin*, 1901, xii, 293.

of tubercles and tuberculous granulation tissue back into the cortex. It is quite evident that in some cases, however, the lesion begins definitely by erosion of the papilla even in the absence of tuberculous disease of the rest of the urinary tract. The end results of all these processes as they appear at autopsy or at operation are usually too far advanced to permit of any clear recognition of their mode of origin. The commonest form is that in which the pyramids are hollowed out into ragged cavities lined with caseous granulation tissue and widely open into the pelvis which itself, with the ureter, is thickened, indurated, and lined with the same caseous granulation tissue or eroded by deep ragged ulcers. In the kidney the excavation, preceded by the new formation of tubercles and granulation tissue, proceeds until the kidney is enormously enlarged into a lobular sacculated mass the wall of which contains only remnants of the much changed cortex. Occasionally the process may make even greater strides and give rise to a perirenal tuberculous abscess or to a fistula extending outward to the skin.

When the patient's power of resistance is great, there may be a more effective production of scar tissue and the caseation is consequently less rapidly destructive. One specimen of this type showed an enormous enlargement of the kidney to which the thickened capsule was densely adherent. The whole organ was practically converted into a translucent fibrous tissue in which there were numerous relatively small pyramidal caseous areas. Another showed rounded caseous areas in the substance of the kidney well encapsulated and sharply separated from the kidney tissue. In the ureter the ulceration proceeds from the formation of lenticular erosions to the enormous thickening of the wall which comes to be lined by a ragged caseous granulation tissue.

Bladder.—Miliary tubercles may occur in the mucosa usually about the trigonum or at the beginning of the prostatic urethra. In other cases lenticular erosions occupy much of the mucosa in these areas. Later they become larger and deeper with irregular ragged margins and caseous lining and may involve the muscularis or extend to the ureteral orifices so as to interfere with their valve-like arrangement, and by rendering them more rigid perhaps aid in allowing the passage of infected material in the reverse direction. The urethra may in rare instances be ulcerated to the meatus. The flat ulcers are, as elsewhere, covered with a caseous layer and extend to only a slight depth. Tuberculous ulceration of the glans penis has not been seen even in those cases in which an extensive genito-urinary tuberculosis existed but has been frequently reported, usually as a consequence of infection during the ritual of circumcision from the saliva of the person officiating. The possibility of infection by coitus with a woman with genital tuberculosis has been suggested, but Franck in a critical review of the literature could find no credible instance of this.

Prostate, Seminal Vesicles, Epididymes, and Testicles.—In a great proportion of the cases of genito-urinary tuberculosis the lesion is most advanced in the epididymis, and indeed tuberculosis of the testicle appears to be almost always due to extension therefrom. The bacilli lodge under the epithelium of the tubules of the epididymis and quickly

produce tubercles which undergo caseation so that the lumen is choked. The whole structure becomes greatly enlarged and on section appears as a twisted sac filled with cheesy material. In the testicle there may be scattered tubercles in and between the tubules or rather widespread caseous areas. The same process of development of tubercles underneath the epithelium with subsequent caseation and ulceration may be followed in the vasa deferentia, and in the seminal vesicles. The latter sometimes retain their form with thickened caseous walls, but in other cases are distended and choked with cheesy material. In the prostate it is unusual to find clear-cut tubercles, but caseous patches form throughout the gland and sometimes by discharge of their contents leave it riddled with cavities.

There has been much discussion of the mode of distribution of these various tuberculous lesions, and there still remains some doubt in the matter, for while many authors incline toward the belief that ascending tuberculosis of the kidney may occur in the way recognized in the case of ascending pyelonephritis caused by other organisms, the surgeons particularly have come to regard tuberculosis of the kidney as almost always due to infection carried by the blood stream. Most enlightening are the recent papers of Sawamura[1] and Walker,[2] which deal with experimental and statistical studies.

From the work of these authors it is clear that primary tuberculosis in the genito-urinary organs occurs practically only in the kidneys and epididymis, where it is common. In the kidneys, Walker thinks the glomeruli the usual seat of the first lesion. Primary tuberculosis of the bladder, prostate, seminal vesicles, vasa deferentia, etc., is so rare as to be of little practical importance. Sawamura was unable to infect the bladder without retention and traumatism, but Walker found the mere introduction of virulent bacilli sufficient. Extension from tuberculous lesions of the bladder is rare, and occurred in only two cases in Walker's long series of experiments. It is possible, however, if contraction of the bladder takes place when the infected urine is kept under a high pressure and especially when the ureteral orifice is eroded. There is no proof of the occurrence of a transmission of tubercle bacilli from bladder to kidney along the lymphatics of the ureter, although that is theoretically possible; and although the direct injection of bacilli into the lumen of the ureter produces renal tuberculosis, the general conclusion is reached that the process in the great majority of cases progresses from the kidney to the bladder and not in the opposite direction. So, too, while there are rare instances in which we must believe the prostate and seminal vesicles to be primarily affected, experimental and anatomical studies show that lesions there, as well as in the vasa deferentia and testes, usually arise by infection from the primary lesion in the epididymis. It is true that the prostate may be infected from the urine or by extension from an adjacent lesion, and so too may the seminal vesicles. Antiperistalsis in the vasa deferentia

[1] *Deut. Zeits. f. Chirurgie*, 1910, Band ciii.
[2] *Johns Hopkins Hosp. Rep.*, 1911, xvi, 1.

in coitus may transmit bacilli from the infected prostate or seminal vesicles, but in general these things are rare, and it remains true that the kidneys and epididymes are the great primary sources of extension in genito-urinary tuberculosis.

Female Genitalia.—Tuberculosis of the female genitalia has been described as a primary affection, but it is usually found as a sequence of tuberculous lesions elsewhere.

The *external genitalia* are sometimes affected, lupous-like nodules of a bluish color, prone to ulceration, being formed about the labia and introitus. The *vagina* is relatively very resistant, and lesions there are practically always in association with others of the uterus and tubes. In the *uterus* itself the mucosa of the body is by far more commonly affected than that of the cervix or portio vaginalis. The lesions may be in the form of discrete nodules in the mucosa, which is converted into a thick, caseous layer, which extends deep into the muscle. The *Fallopian tubes*, of all parts of the genital tract, are most commonly tuberculous. The usual lesion consists in great thickening and rigidity of the wall, with destruction of the whole mucosa and the caseation of the lining layer of tuberculous granulation tissue. The complete occlusion of the tubes by this material accounts for the almost invariable sterility of women with genital tuberculosis.

The *ovaries* are less commonly tuberculous. When affected the lesion consists of caseous areas in the stroma and usually is not connected with the follicles. Tuberculosis of cysts in the ovary has been observed.

Extensive adhesions about the tuberculous pelvic structures and a tuberculous peritonitis are very common accompaniments of the condition. However, tuberculosis of the bladder and kidneys occurs in this connection by no means so frequently as in genital tuberculosis in males. This is easily understood on account of the less intimate anatomical association of the organs in the female.

As to the pathogenesis of the condition the question arises at once as to the mode of extension of the infectious agent. There are those who regard the direct infection of the vagina and uterine cavity by the use of infected instruments, etc., and by coitus with a tuberculous man as a prominent factor; but while such a possibility cannot be denied, the weight of evidence is not in favor of this view even in married women, to say nothing of virgins and children, in whom the condition frequently occurs. The bacilli may be carried to these organs by the blood stream from an older focus elsewhere, and this idea is the most widely accepted. Why the tubes should be most frequently the seat of the lesion and show more extensive changes than the rest of the tract is not clear, but it may perhaps be regarded as a specially favorable tissue for the growth of the bacillus.

Tuberculosis of Various Glands.—Breast.—The breast was formerly thought to be immune from tuberculosis, but is now known to be affected not infrequently. Several possible paths for the entrance of the bacilli into the tissue have been pointed out, of which the blood stream and efferent ducts are perhaps most important. Cases have been reported in which caries of the ribs or a tuberculous pleurisy has by extension given rise to the infection, and others have believed that in cases in which

the axillary glands were swollen and caseous the infection may have travelled backward along the lymphatics from those glands. It seems more probable, however, that the tuberculosis of the axillary glands may have been in those cases secondary to tuberculosis of the breast. The disease has not been observed in children before puberty. It occurs chiefly in women, but has been seen in men. It may affect all ages, but is much favored in its development by pregnancy and lactation, and most frequently affects women in the prime of life. The lesions are found in the form of discrete, caseous nodules, usually in the interstitial tissues, or as large, abscess-like areas in which the semifluid content has resulted from the destruction of a great deal of tissue.

Spleen.—Tuberculosis of the spleen, notwithstanding that there have been descriptions in the literature of a primary affection, may be regarded as always secondary to tuberculous lesions of other organs and the mode of entry of the organisms is doubtless always by the blood stream. In practically all cases of disseminated tuberculosis tubercles are found in the spleen. These may be miliary, but it is well recognized that such lesions tend to reach a relatively great size in the spleen as compared with the liver and various other organs. Such conglomerated tubercles rapidly undergo caseation and stand out prominently against the surrounding dark red pulp as rounded, opaque, yellow masses.

Thyroid Glands.—The thyroid, long held to be almost immune from tuberculosis, has been shown in recent years to possess no such complete immunity, although it is true that tuberculous lesions of the thyroid are uncommon, primary tuberculosis of this gland being especially rare. In autopsies on tuberculous individuals Chiari has found in 100 cases 7, Fränkel in 50 cases 5, Simmonds in 100 cases 3, and Hegar in 1563 cases 57 cases of tuberculosis of the thyroid. It appears usually in the form of scattered miliary tubercles in the course of an acute general miliary tuberculosis, but sometimes as a localized tuberculosis with caseous nodules. Roger and Garnier and other more recent writers, including de Quervain and his student Sarbach, have emphasized the occurrence of a general sclerosis of the thyroid in cases of tuberculosis in which there are no actual tuberculous lesions of the gland itself.

Adrenal Glands.—The adrenal glands show no such relative freedom from tuberculous lesions, but are frequently affected, scattered miliary tubercles being perhaps less often described than larger, caseous areas, which produce great destructive changes. Isolated tuberculosis of the adrenals has been described several times, probably as the result of some inconspicuous primary lesions, but it forms, as a rule, part of a more generalized affection. The caseous areas appear as opaque, yellow patches in the enlarged gland, involving both cortex and medulla, and not infrequently including the associated sympathetic nerve structures. In some cases there is an attempt at encapsulation, and very large masses of necrotic material may extend beyond the normal limits of the gland, surrounded by fibrous tissue, their relations being recognizable only by the persistence of small portions of the gland substance. In other cases the tuberculous lesion may be shrunken to a small, scarred, calcified area, buried in adhesions with surrounding organs.

Interest in tuberculosis of the adrenals depends chiefly upon the symptom-complex of Addison's disease so frequently associated with it. It is quite true that any other change which destroys the adrenals gradually will bring about this disease, and, further, that there are many cases of tuberculosis of the adrenals in which a great part of the gland is destroyed without any such symptoms; so that it is really not known which of the various constituents of the gland are responsible for the symptoms. The theory of Wiesel that the appearance of these symptoms depends upon the destruction of the whole chromaffine system, which is constituted by cells in the sympathetic ganglia and in the medulla of the adrenal, while the cortex of the adrenal is not concerned, is tempting, and goes far to clear up the inconsistencies of various cases, but his observations have not yet been widely confirmed.

Tuberculosis of the Central Nervous System.—While cases of tuberculous affection of the brain and meninges are of rather common occurrence, they form a relatively small proportion of all cases of tuberculosis.

Brain.—The most common form of tuberculosis of the brain is that which affects chiefly the meningeal covering, the pia of the base of the brain being the portion which usually shows the most extensive alteration. Nevertheless, the tubercles there are very often associated with others in various parts of the brain. It is thought that the tubercle bacilli are brought there by the blood stream, and Hektoén traces the development of the tubercles from the inner walls of the bloodvessels; they soon affect, however, the whole tissue of the meninges, and there is usually to be found, on examination of such a brain, a thick, yellow, opaque exudate over the basal portion covering the pons, the medulla, and the optic chiasm, and extending in the sulci along the course of the vessels toward the upper surface of the brain. Close inspection will reveal small, gray nodules embedded in this exudate, and arranged along the course of the bloodvessels. These are often especially clearly seen on pulling aside the temporal lobe and examining the vessels in the Sylvian fissure. These lesions, which are accompanied by hyperemia of the tissues, usually fade away to a great degree as one passes toward the surface of the cerebral hemispheres, and over the spinal cord they are also usually less intense.

Microscopically, one finds in those cases which have developed very rapidly a considerable percentage of polymorphonuclear leukocytes in the exudate, but usually it is composed chiefly of polyblastic cells of various forms, all members of the series being found, from the numerous small cells to the very large, actively phagocytic cells with large, vesicular nucleus and abundant protoplasm. The bloodvessels are especially affected, their walls being eccentrically thickened by masses of new-formed tissue of tubercle-like structure, which have developed chiefly in the adventitial coat; less advanced new formation of tissue is evident in the intimal coat, the media being passively encroached upon from both sides. This mass of epithelioid cells, usually without definite giant cells, is very prone to caseation with fragmentation of the nuclei, and hence the opacity of many of the nodules seen along the vessels. Partial or complete obliteration of the affected vessels is not uncommon.

Similar changes are frequently found in the *ependyma of the ventricles*, where definite minute tubercles often appear. These are visible as tiny grains upon the choroid plexuses and are not to be confused, as Ophüls has pointed out, with the minute, dense nodules found in the same position in ependymitis granularis, which occurs with various chronic diseases. They are often accompanied by an abundant exudate of fluid, with wandering cells and fibrin, which produces the internal hydrocephalus, thought by some writers to be so characteristic of tuberculous meningitis. The amount of fluid varies greatly, but in most cases is not great. Tuberculous meningitis is frequently associated with allied lesions of the brain itself, when the condition may best be described as tuberculous meningo-encephalitis. These changes in the brain consist in the presence of caseous tubercles in the brain substance, usually just under the meninges and continuous with the tubercles in the meninges, but they may be deeply embedded in the tissue of the brain. In general, such tubercles are relatively large, and appear as rounded, yellow areas of opacity surrounded by a zone of red. Sometimes, and then often without any associated meningitis, there may be but one or two caseous masses. These solitary tubercles may reach a great size, and in two cases seen recently there were tumor-like structures of the size of a hen's egg occupying the greater portion of the cerebellum, leading to symptoms of ataxia. Composed chiefly of caseous material, the margins of these masses exhibited beautiful tubercles with giant cells, partly obliterated tuberculous bloodvessels, and tubercle bacilli. Such large tubercles are sometimes seen in the spinal cord. The nerve roots are also sometimes involved, and in a recent case extensive paralysis of the lower portion of the body was due to the invasion and destruction of nerve roots by tubercles developed within the dura.

Tuberculous lesions of the *dura* are usually produced by extension from caseous areas in adjacent bones, and are, as a rule, localized in that neighborhood.

Tuberculosis of the Bones and Joints.—In all instances except in those in which the skeletal structures are encroached upon by tuberculous processes arising in adjacent tissues the bacilli must be brought to them by the blood stream, and it is practically certain that such bacilli come from some primary lesion which may be so small as to be overlooked or may be healed when the osseous lesions have developed.

Such osseous lesions arise very frequently in young children, but are by no means uncommon in more advanced age. They affect most frequently the short bones in which cancellous tissue is abundant, such, for example, as the vertebræ, the carpal and tarsal bones, and the epiphyseal portions of the long bones, while the diaphysis of these latter and the bones of the skull are less commonly their point of origin.

Beginning in the cancellous bone as grayish-red, translucent infiltration, the process soon extends with the formation of many tubercles and a tuberculous granulation tissue among the marrow spaces. This is usually associated with both rarefaction and eburnation or induration of the bony material, the inflammatory process promoting in places the excessive new formation of the bone, while the neighboring bony trabeculæ

are eroded and thinned out. Caseation follows, often with the complete destruction of the affected area, sometimes with sequestration of the indurated part. A cavity is formed filled with soft, yellow, caseous material, often containing fragments of necrotic bone. Exceptionally such a focus may heal spontaneously, but usually it advances either toward the diaphysis of the bone or more commonly toward the articular surface and the joint. In early life the destruction of the epiphyseal cartilage by such disease may seriously limit the growth of the bone, but probably more important is the limitation of growth and actual atrophy which results from the inactivity of the limb.

Extension of the tuberculous process into a joint is followed by different results, according to the rapidity of advance. If the joint be invaded while in its normal general condition a dissemination of bacilli throughout its cavity usually results, and the development of an exudate of serofibrinous character, which may then be absorbed and followed by the growth of a tuberculous granulation tissue over the synovial surface. This may in time become very thick and translucent, and is often accompanied by a great accumulation of fluid, and by marked œdema or fibrous induration of the tissues about the joint (*e. g.*, the so-called white swelling of the knee), or without much or any exudation of fluid the tuberculous granulation tissue may rapidly undergo caseation and erosion. The cartilage of the joint is entirely passive and may be lifted up and dislodged over a caseous focus in the bone, or may undergo a softening with loss of its elasticity, so that it in some cases becomes actually "smeary" in consistence and is soon destroyed by the apposed ends of the bones. In such cases the exposed and partly caseous bony ends are often crushed into one another and extensive deformity is produced. Often before the caseous focus in the bone reaches the joint, the synovial cavity has become obliterated in part or completely by inflammatory adhesions, so that there is no longer a question of a synovitis, but the tuberculous process continues to extend from one epiphysis to the next.

Other cases progress much more slowly and there is time for extensive new formation of tissue in and about the joint, not only in the form of exostoses which often limit the mobility, but also in thickenings and villous outgrowths from the synovial membrane itself. Degenerative and mechanical compression of the fibrinoid synovial outgrowths produces in some cases the pedunculated or free corpora oryzoidea, or rice bodies, which are smooth and of about the size and form of a melon seed. Tubercle bacilli have been demonstrated in them. In other instances the so-called lipoma arborescens results from the great overgrowths of the tissue of the joint, producing polypoid branched structures sometimes several centimeters in length. These are composed largely of fat, but usually contain tubercles. Usually, the active destructive processes in the joints, leading to the loss of the synovial membrane and the cartilage and the erosion and crushing of the ends of the bones, are not confined to those tissues, but the adjacent structures become involved, and not only is there œdema and cellular infiltrations and induration of those tissues, but sinuses and fistulæ are formed which burrow along the fasciæ, often to a great distance, until they reach the skin. A bluish,

abscess-like swelling shows itself for a time, and finally opens to give drainage through the tortuous channel to the caseous debris.

Extensive collapse and displacement of the bones may occur in the rapidly progressing cases, so that, for example, while the head of the femur remains fixed in the acetabulum, the caseous neck breaks and the trochanteric end of the femur becomes dislocated to a point high upon the pelvis, with great shortening of the leg, This destruction is perhaps most frequently seen in the vertebræ, where caseous areas develop usually first under the anterior ligament, producing a prevertebral abscess, but quickly extend to soften and destroy the cancellous bone. This allows of the collapse of the centrum, with the angular deformity of the spine; when only one centrum is affected the spinous projection in the back is a sharp one; if a number of vertebræ are destroyed there is produced a rounded kyphosis. From such a vertebra with its prevertebral abscess similar sinuses are often seen to burrow their way down through or beneath the psoas muscles until they can appear at the skin in the groin or on the inner side of the thigh.

Periosteal tuberculosis, as, for example, in the ribs and other bones which lie near the skin, may give rise to quite large accumulations of exudate and caseous material, often termed cold abscesses.

As to the pathogenesis of the bone and joint lesions of a tuberculous nature it may be said that in many cases it is impossible from the advanced stage of the disease to tell whether bone or joint was first affected. König maintains that the synovial cavity is always first infected, but Guillemin and many others hold the opposite view and support it by statistics, which show that in the majority of cases the adjacent focus in the bone gives rise by its extension to the infection of the joint.

Tuberculosis of the Muscles, Tendons, and Fasciæ.—The muscles, tendons, and fasciæ are generally involved in tuberculous processes as the result of extension of the lesion from an adjacent caseous area in bones or elsewhere, but cases have been described in which isolated hematogenous foci were found embedded in the muscle. The lesion produces cavities in the muscle filled with a soft, caseous material, and lined with a tuberculous granulation tissue with giant cells of the usual character. The muscle fibers in the immediate vicinity are in large part atrophic, but some are greatly enlarged. Various French authors, among whom Hemery may be mentioned, distinguished three forms: the cold abscess of muscle, disseminated tuberculous myositis, and tuberculous muscular sclerosis.

Bursæ.—Isolated tuberculosis of bursæ may also occur, but are usually a sequence of tuberculosis of adjacent bones and joints. Schuchardt describes three forms of tendon-sheath tuberculosis which closely resemble those seen in joints, namely, tuberculous fungus of the sheath, in which the lining is covered with a tuberculous granulation tissue, a nodular form in which a persistent, tumor-like, gray, non-caseating mass is formed, and finally the rice-body hygroma analogous to the similar change in the joints.

Tuberculosis of the Skin.—Much confusion still seems to exist in the classification of tuberculous lesions of the skin, and there are several

affections the tuberculous nature of which is still a matter of doubt. Distinctly tuberculous are those forms known under the names lupus, scrofuloderma, tuberculosis ulcerosa, and tuberculosis verrucosa cutis, to which Kaposi has added another group with the designation tuberculosis miliaris cutis. Besides these there are certain affections, such as lichen scrofulosorum and lupus erythematosus, which frequently occur in association with tuberculosis, but the strictly tuberculous nature of which is not yet decided.

Lupus, which by some authors (Unna) is divided into circumscribed and diffuse forms, is an affection of the skin produced by infection from without, and not necessarily associated with tuberculosis of the internal organs or underlying tissues. The lesions occur either in the form of pale brownish or bluish, non-vascularized nodules, sharply marked off from the adjacent normal skin, or as spreading hyperemic areas elevated above the surrounding surface, and showing their brown pigmentation only when the bloodvessels are emptied by pressure. All possible transitions between these forms occur with various modifications produced by the excessive growth of the epidermis, etc. They appear usually upon the exposed surfaces of the body, as, for example, in the skin over the nose and cheeks. The course of development is usually slow, and the lesions are extraordinarily persistent, reappearing often after they had apparently undergone healing. Ulceration is frequent, with extensive destruction of the tissue and subsequent scarring.

Histologically, these nodules are composed of tubercles quite similar to those seen elsewhere, developed in the skin sometimes in the form of compact, non-vascularized nodules, at other times as a sort of vascular granulation tissue studded with tubercles. Tubercle bacilli can be demonstrated in this tissue, which proceeds to caseation, and in that way to the formation of ulcers in the skin. The localized nature of the disease may often be shown by the possibility of bringing about healing.

The term scrofuloderma is applied to those tuberculous lesions of the skin which are directly produced by underlying tuberculous foci in bones, joints, lymph glands, and other tissues. Such are the changes described above as resulting from the extension of sinuses from tuberculous foci in bone to the skin. They appear at first as soft, fluctuant elevations of bluish-red color, which finally break down and, liberating a quantity of caseous material, remain permanently open. Such deep cavities are lined with an abundant tuberculous granulation tissue, the caseation and ulceration of which often extends widely to the neighboring skin. This, as is evident from the description, is a lesion of the skin of distinctly secondary nature. The third form, tuberculosis ulcerosa, is less common, and appears in individuals suffering from severe visceral tuberculosis as ragged, superficial ulcers in the mouth and adjacent skin, about the external genitalia, etc., evidently due to an auto-inoculation.

Rather different in character from these is the verrucose form of the disease, which is due to direct infection of the hands, in most cases from contact with tuberculous materials. The nodules are often spoken of as necrogenic tubercles, or "Leichentuberkeln," on this account. Appearing as nodules covered by a much thickened and keratinized epidermis,

and formed in the depths of the skin of an infiltrated connective tissue with tubercles, these areas often tend to heal spontaneously. They are in many instances later associated with widespread internal tuberculosis, but on the whole they present a mild form of the cutaneous tuberculous affection. They cannot be very sharply separated in any classification from the cases of lupus.

The miliary form of tuberculosis of the skin which Kaposi has recently emphasized has been long known as a part of a generalized miliary tuberculosis occurring in the form of multiple, scattered nodules of a tuberculous nature in the skin, and tending to caseation and ulceration.[1]

As to the affections mentioned above, which are frequently associated with tuberculosis of the internal organs, it may be said that while it cannot in most cases be demonstrated that lichen scrofulosorum and lupus erythematosus are anatomically tuberculous in nature, it is thought by many that they may be the expression of the effect of the toxins of the tubercle bacillus upon the skin (Hallopeau).

Jacobi, Riehl, and others have demonstrated tubercle-like structures in cases of lichen scrofulosorum with giant cells, but these are not typically tuberculous, and the bacilli have not been definitely demonstrated; inoculations were negative. Interesting, although not conclusive, evidence in favor of their tuberculous relations is found in the fact that they react to tuberculin injections in much the same way as the lupus nodules. Practically the same doubts exist as to lupus erythematosus, and Jadassohn is forced in respect to it, as in the case of lichen scrofulosorum, to leave the question undecided after considering the evidence on both sides.

[1] Tileston, *Arch. Int. Med.*, 1909, iv, p. 21.

CHAPTER VI

THE SYMPTOMS, DIAGNOSIS, PROGNOSIS, PROPHYLAXIS AND TREATMENT OF TUBERCULOSIS

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THE SYMPTOMS OF TUBERCULOSIS

In some cases pulmonary tuberculosis is almost entirely a disease of symptoms; in others, it is true, of physical signs, but these are far in the minority. The symptoms can be grouped in two classes: first, the general, and second, the localizing symptoms. The general symptoms are often not sharply defined and may be so slight as to escape the patient's notice. They are of less importance in localizing but of more importance in determining the presence of the disease. The relative importance of these symptoms is difficult to determine, but none is of greater value to the physician than fever.

Fever.—Fever may precede all other symptoms and few patients are apyretic throughout the entire course but most incipient cases are, however, afebrile as soon as their lives are well regulated. The fever is characterized by chronicity, post-meridian occurrence, a daily maximum usually at the same hour, occurrence in attacks which may supervene upon a normal or slightly elevated temperature and often by remarkably slight constitutional disturbance.

It is of the greatest importance to know the temperature of each patient. He should be provided with a good thermometer recently tested, and a little care in teaching him how to take his temperature is invaluable. If taken by mouth, in cold weather he should be in a warm room for ten to thirty minutes with his lips closed. If taken by rectum, it is wise not to take the temperature soon after a stool, or for thirty minutes following exercise. Menstruation and pelvic inflammation may affect the rectal more than the oral temperature. Rise of temperature is usually perceptible earlier by rectal than by oral measurement. Without doubt the rectal temperature is more accurate and less subject to minor variations. In patients with fever the difference is always most marked for the lower temperatures and least for the higher.

The temperature should be taken every two hours, beginning on awakening, until the medical adviser is fully acquainted with the range. Then if the temperature be normal it may be taken on awakening, at the time when the daily maximum occurs, and at 8 P.M. In neurotic patients as little attention as is consistent with proper treatment should be paid to the temperature. This consists, in afebrile patients, of taking the

temperature for two days every two to four weeks, and during the interval if there is the slightest suspicion of fever. If the patient cannot sleep or has headache he should take his temperature during the night, as in some cases the rise occurs at night only, or a second rise may occur at that time.

During rest in bed the rectal temperature may be said to be normal when it varies between 97.3° and 98.5° on awakening, 98.6° and 99.1° in the forenoon, and 99.1° and 99.5° in the afternoon. In some cases, however, it may reach nearly 100°. The oral temperature rarely sinks below 97° in the morning and seldom goes above 99.2° in the afternoon or evening. Exercise affects the rectal temperature much more than the oral. Simply getting out of bed in the morning may raise the rectal temperature some tenths of a degree, and after exercise a rectal temperature of 101° or over has been frequently recorded in apparently normal individuals. A rectal temperature of 100.4° immediately after exercise is not to be considered abnormal. The oral temperature rarely shows much elevation after exercise and may be lowered for some time on account of the cooling influence of the more rapidly respired air.

Cause of Fever.—This is primarily the effect of the changed or unchanged tuberculous protein, absorbed from the tuberculous focus, upon the heat centre, rendered no doubt more irritable by previous contact with the same irritant in doses too small to cause fever. The fever produced by the injection of tuberculin proves that secondary organisms and their products are not necessarily its cause. The fever late in the disease, the hectic or absorption fever, may be due in part at least to the absorption of bacterial proteins other than those produced by the tubercle bacillus and to the absorption of necrotic matter from softening foci.

The temperature curve with its daily rise or rises can be readily explained by the effect of bodily exercise upon absorption. The absence of fever after the long rest at night is thus explained as well as the afternoon rise after the exertion of the morning. No doubt this explains also the rise of temperature at night in some patients with severe cough on lying down. Absorption, therefore, plays an important part, and the higher fever in acute tuberculosis or in acute attacks is due to the greater absorption through the more patent lymph channels. It has long been recognized that the disease in patients with fibroid phthisis or with chronic cavity formation may be afebrile, although advancing. In other cases fever occurs only when the outlet of the cavity is plugged or when fresh areas with patent lymph channels are involved. Fever caused by overexertion may not occur for several days.

Fever in Chronic Pulmonary Tuberculosis.—Every known type of fever may occur, but the usual temperature curve is one which is normal or slightly subnormal in the morning and rises to 99.5° or 100° (by mouth) between noon and 9 P.M. The fastigium lasts usually for two or three hours, but may be so short that it is recorded only when the temperature is taken every two hours. As a rule, the maximum is between 3 and 5 P.M., the minimum between 2 and 4 A.M. Many patients have a slight rise for months before their attention is called to it by some other symptom. As the disease advances the febrile attacks are sharper and in some

instances more protracted, but the acute exacerbations of fever are often of ten to fourteen days' duration, the time which is required in experimental tuberculosis for the formation of antibodies. In still more advanced stages, fever is present at some time every day, and may be continuous, intermittent, or, as is more usual, remittent. The temperature seldom exceeds 104°, but is frequently subnormal. A fall of temperature is often observed after the formation of a cavity. In many cases, however, the temperature goes from normal or slightly below to 100° or 101° with great regularity.

It must not be expected that the temperature curve will always follow the course just outlined, undisturbed by other causes. Complications, tuberculous and non-tuberculous, as well as an advance of the tuberculous process in the lungs, may cause fever. A sudden and sharp rise without warning rarely occurs in the ordinary progression of the disease.

The temperature of the tuberculous patient is very unstable, due in part at least to the effect of the tuberculous poison upon the nervous system, especially upon the heat-regulating centre. A slight mental excitement or slight physical exercise causes more rapid heart action and increased stimulation of the heat centre, either from the increased poison in the blood or from an increased amount of poison in contact with the heat centre. However this may be, the tuberculous invalid is prone to rise of temperature from trivial causes. The rise of temperature in 50 to 60 per cent. of patients from one to seven days before or during the menstrual period and the "digestion fever" said to occur in some patients, usually anemic, after the chief meal of the day, are due, no doubt, to this lability of the temperature.

Rise of temperature, if of any duration and not due to complications, indicates activity in the pulmonary lesion. The disease, however, can progress without discoverable rise of temperature, although this takes place usually only when the individual has no longer sufficient powers of resistance. As a rule, the degree of activity can be told from the temperature chart. Even slight rise of the minimum temperature is to be regarded as suspicious of increased tuberculous poisoning, while the maximum temperature usually shows the intensity of the disease or possibly the activity of the secondary organisms. High intermitting fever indicates a severe and deep-seated lesion and often quick destruction of tissue. Fever may occur and the patient show all signs of increased activity, but several days may elapse before any increase in the physical signs becomes evident. In fact, some patients recover from the febrile attack before the lesion causing it is discovered. A rise to 106° or 108°, if present at all, usually occurs shortly before death, but in the writer's experience it is much more common for the temperature to fall below normal for a day or two before death. The temperature on the two sides of the body may vary and is higher usually on the side affected.

Fever in Acute Pulmonary Tuberculosis.—In these cases fever is usually a marked symptom and may closely simulate that of typhoid fever, pneumonia, or in rare instances suggest malaria. The temperature curve, however, seldom closely simulates a single tertian infection. In a few cases the rise extends over a period of two days to become normal

on the third. This may be repeated a number of times. In most cases of acute tuberculosis the temperature is continuously high, with but slight morning remissions.

In acute miliary tuberculosis, either primary or secondary, the temperature is usually high, continuous, with very slight morning remissions, and may range between 102° and 105° for days. Marked remissions with a normal temperature of several days' duration may occur. The "inverse" type of temperature, said to be the only curve due solely to the tuberculous poison, is rarely observed either in this or other forms of pulmonary tuberculosis. In acute pneumonic tuberculosis the temperature curve is at times similar to that of typhoid fever in the second week, or pneumonia, but more often it resembles typhoid in the third or fourth week, with more or less marked remissions. The temperature usually ranges from 100° or 101° to 103° or 104°.

Fibroid tuberculosis may occur with slight or no elevation of temperature, or the temperature may be subnormal.

Some affirm that the presence of mixed infections can be told from the temperature and that the "streptococcic" curve is characteristic. In the morning the temperature is often markedly subnormal, and Lebert records one case in which it reached 89°. In the afternoon or evening the temperature rises rapidly to from 101° to 104°. A variation of 4° or 5° is frequent, and as much as 14° has been observed. Uncomplicated tuberculosis of the serous membranes may produce a hectic fever.

Weight.—Loss and Gain.—Wasting has long been recognized as most characteristic of pulmonary tuberculosis, termed for this reason "consumption" or "phthisis." It stands usually in direct relation to the stage and chronicity. This affects all the organs except the liver, which may undergo a fatty change, and possibly the bones. The fatty and muscular tissues are most affected. Loss of weight may be the most prominent and in a few cases the only symptom. It may occur so gradually that it escapes attention for some time, or it may be very rapid in the early as well as in the later stages, but those with slowly advancing disease may lose little or no weight. Loss of weight is in proportion to the duration of the disease, and young patients lose more rapidly than older. The "normal" weight of patients with pulmonary tuberculosis is about ten pounds less on an average than what they should weigh. Loss of weight is due to the effect upon cell nutrition in general of the poison absorbed from the pulmonary lesion. This, affecting simultaneously all the systems, causes directly a deficiency in the digestive ferments (Hays) and a loss of appetite and so prevents repair of the normal waste of the body. This favors extension of the disease, increased poisoning, and in time the cellular protoplasm gradually loses its power of regeneration, which late in the disease is accentuated by vomiting and diarrhœa. The poison also produces fever, which causes increased metabolism and hastens loss of weight, but this is not dependent upon fever, as it may occur in the absence of this symptom. The loss of weight occasioned by nervous excitement and exercise can be explained by the increased absorption of poison.

Loss of weight in chronic disease may amount to one-third to two-fifths of the previous weight. If a patient lose one-fourth of his normal theoretical weight his nutrition is apt to be considerably disturbed and a loss of one-third is a grave omen. A larger percentage of weight can be lost by fat individuals. Great emaciation is rarely present in acute disease. The greatest loss recorded is 130 pounds in a man weighing 271 pounds in health. A loss of 5 or 6 pounds a week is not unusual for a short time.

Gain in Weight.—This depends not upon ingestion, but upon assimilation. Patients who are so fond of meat that little else is eaten are less likely to gain than good general eaters. Many patients who have had high fever gain in weight when the fever decreases, although a continuously elevated temperature may still be present. Gain in weight, if much loss has occurred, is practically a necessity for improvement. Change of climate is not so essential in the case of the poor as good hygienic conditions. Many patients in advanced stages gain in weight for three or four months after a change of climate, but then gradually lose.

Cold seems to have a marked influence upon weight-gaining in the healthy as well as in the tuberculous. The weight curve in pulmonary tuberculosis, if not influenced by change of climate or other factors, rises from August to Christmas (sometimes to November), remains more or less stationary with minor fluctuations from Christmas to Easter (March), and sinks gradually from Easter to August. This corresponds closely with the normal weight curve and is based upon a study of the weight charts of 1200 patients at the Adirondack Cottage Sanitarium. Some patients at rest gain little, but put upon carefully regulated exercise begin to gain at once.

The average gain of weight under treatment depends upon whether or not forced feeding is employed, the activity of the symptoms, and the amount of weight that has been lost. Patients with far-advanced disease and considerable loss of weight usually gain more on an average when the disease becomes quiescent than those with advanced but less than those with incipient disease. The largest gain in weight that has come under the writer's notice occurred in a man with a cavity and rather extensive disease on one side, and a slight affection of the opposite apex. Returning to his work against advice, his weight fell from 145 to 115, and his lung condition became worse. During a second sojourn of two years his weight increased to 230 pounds. In 2 patients, in early stages, without much loss of weight, gains occurred respectively of 15 pounds in fifteen days and 27 pounds in twenty-eight days. A gain of 2 pounds a week is satisfactory. Weight may be gained irregularly, *i. e.*, a gain may occur on the first and third days and a loss on the second. The mental condition directly affects the weight. The gain in weight in many cases occurs first on the chest and face, but is most marked on the hips in women and abdomen in men. Men, as a rule, lose more and gain less than women.

The *persistence of the gain in weight* is often remarkable. In some cases (about one-third, Berger) the gain is continued when the patient returns to his home and lives properly. Weight gained during exercise is more permanent than weight gained at rest. Weight acquired through a

liberal use of milk and eggs, especially if without exercise, is often quickly lost.

Metabolic Changes.—**Salts.**—The excretion of calcium phosphate as well as of lecithin and nuclein is increased, and Mitulesku finds the phosphorus output parallel with the nitrogenous. Magnesium and calcium salts are increased in the terminal stages, especially when fever and loss of appetite are present (Ott). The "demineralization" of the French observers is not peculiar to tuberculosis, but occurs first and irregularly in later stages. Ferrier holds that phosphaturia and tuberculosis are closely related. Decalcification, he believes, is of much importance, and should be vigorously combated. This work still lacks sufficient confirmation.

The excretion of ammonia and of indican, when cavities become septic, is increased. The different phenols and skatols are also increased in destructive processes. Urobilin is increased usually, but in very acute processes is decreased.

Respiratory Exchange.—The gaseous exchange in the lungs, in spite of marked destructive processes, undergoes practically no alteration.

Loss of Strength.—This often occurs as the primary manifestation, but is rarely recognized as such at the time. Many patients begin early to tire easily, and work which once was a pleasure begins to drag. This debility may be present to a very marked degree and out of all proportion to the extent of the discoverable lesion. A point often mentioned by the patient is that while he seems to have as much muscular power as ever for a single act, he is incapable of sustaining for any length of time muscular or, in some cases, mental work. The general muscular tonicity has been found to be greatly diminished in the incipient stage, even when the muscular power and nutrition are good. The loss of strength is most probably due to the effect of the disease upon the nervous system.

As the disease progresses and, in fact, often within a few weeks after the patient has "given in," he feels much better. Loss of strength is of course directly proportional to the general condition. Nothing is more deceptive than the robust appearance of many patients undergoing the modern treatment when compared with the lack of strength. The slow return of strength is a most striking feature in many cases and one of no inconsiderable importance in treatment. In far-advanced cases the debility may become extreme, and yet, on the other hand, it is remarkable what many patients, seemingly tottering on the brink of the grave, can accomplish. Stevenson fully recognized this in *Aes Triplex* and in his own life.

Night-sweats.—These, while rare in the early stages, occur more frequently in pulmonary tuberculosis than in any other disease. In a few cases they precede all other symptoms and even physical signs. This, however, is rare, as they are usually associated with fever and a subnormal morning temperature. As the disease progresses, or during acute attacks, the night-sweats become more frequent, and in the later stages drenching sweats are common, and may occur not only at night, but whenever the patient falls asleep (sleep-sweats). The sweating,

so exhausting, so unpleasant, and so depressing that the patient dreads going to sleep, usually occurs early in the morning and possibly not until during a nap following the morning cough.

The sweats vary much in severity. At times so slight as to be scarcely perceptible, they may be so profuse that the night robes have to be changed three or four times a night and possibly some of the bedding as well. Sweats were absent in 10 per cent. of Louis' cases and in 41 per cent. of 2344 cases at the Phipps Institute, Philadelphia. Sudamina, more frequent in acute, rarely occur in chronic cases following sweats. Acute inflammatory processes and diarrhœa may hold the sweats in abeyance for a time. They are less frequent in children, and in patients with diabetes mellitus. Hemidrosis may occur, but is accidental. The night-sweats are general when severe, but the slighter forms are often more localized, and occur most frequently about the head and neck or extremities. The sweat has been found in some cases to give a tuberculin reaction on injection, but never contains tubercle bacilli. The amount of sweat in some cases exceeds twenty ounces.

Cause.—The sweat glands are under the control of centres which can stimulate or inhibit the secretion. Increased blood supply to the skin increases secretion of sweat, and consequently these glands are closely connected with the vasomotor centre. Early in pulmonary tuberculosis, sweating is usually the result of poisoning of the sweat, vasomotor, and heat centres by the tuberculous poison; in the more advanced stage the sweat may be the result of fever, which stimulates the sweat centres, the vasomotor centres (causing dilatation), and the glands; and late in the disease the sweat centres or glands may be stimulated independently of the heat and vasomotor centres by the poisons.

The increased frequency of sweating in acute processes is due probably to the more rapid absorption of poisons. Some hold that overstimulation of the vasomotor (constrictor) centre finally gives way during sleep to a greater relaxation than normal. The increased blood-supply then causes the sweat. The presence of the poison, however, is not always sufficient to cause sweating, and some pathological changes in the circulation and nutrition are generally necessary. The absorption of necrotic matter or pus is, according to some, the chief cause. In most cases the sweat glands respond to slighter stimuli than normally.

Chills.—These may occur early in the disease, and when present daily often give rise to a diagnosis of malaria. They occur usually before, seldom after, the rise of temperature. Following a sweat, chills are not infrequent.

Blood.—The blood picture varies with the stage, the acuteness, and the complications. In patients with incipient disease it is often normal, and during treatment the erythrocytes and the percentage of hemoglobin and possibly the amount of blood are frequently above normal. Other patients are anemic from the outset. The earliest and most constant change is the reduction of the color index, and chlorosis in many instances is masked tuberculosis. A slight diminution of the erythrocytes is frequent in this group of cases, while the leukocytes may be either slightly increased, decreased, or, as is more usual, normal. When the disease

reaches the advanced stage, the pallor of the face, which may be present earlier, becomes often very marked, and is at times in strong contrast with the red color of the lips and mucous membranes. The blood here is often normal in every particular, and the erythrocyte count and hemoglobin may be above normal. The leukocytes are usually very slightly if at all increased. The explanation of this lies in the concentration of the blood and a real leukopenia. The large amount of fluid lost by the increased salivary and bronchial secretions, the night-sweats, and diarrhœa if present, and probably also the action of the tuberculous poison producing an increased flow of lymph to the tissues, are all factors.

Leukocytes.—In acute miliary tuberculosis of the lungs, leukopenia is more often present than leukocytosis. The latter is at times present in caseous pneumonia. In chronic fibroid conditions leukocytosis is usually absent unless a cavity is present. Tuberculous complications, unless accompanied by secondary infection, rarely produce much increase in the leukocytes. During softening a leukocytosis is usually present and it may occur with tuberculous hyperplasia of the glands with slight destructive pulmonary changes. Leukocytosis is said to be a constant accompaniment of cavity formation, and a prolonged absence of leukocytosis is held to exclude this condition. Such, however, is not always the case, especially in chronic cavities (Ewing). Acute tuberculosis supervening upon a leukemia may reduce markedly the number of leukocytes, but chronic pulmonary tuberculosis and leukemia may coexist without reduction in the number of leukocytes.

The differential count shows considerable variation. The polymorphonuclear cells vary between 60 and 95 per cent., but are usually about 80 to 84 per cent. Leukocytosis in pulmonary tuberculosis is almost always due to increase of these cells. Some have tried to show a prognostic value for this type of leukocytosis, believing a low mononuclear count decidedly less favorable than a higher one. In low counts the large and small lymphocytes are usually relatively and possibly absolutely increased. Myelocytes may be present, but mastzellen rarely occur.

The blood-platelets are normal, decreased, or increased. Even in the most advanced stages their number may not be reduced.

Arneth, from a study of the polymorphonuclear leukocytes, found that in health 5 per cent. contained a single nucleus, 35 per cent. two nuclei, 42 per cent. three, 17 per cent. four, and 2 per cent. five nuclei. Other observers have found in health a considerably larger percentage of cells with one nucleus, and more cells with two nuclei. In pulmonary tuberculosis the number of cells with fewer nuclei was much increased. Iodophilia is of little value in pulmonary tuberculosis.

The *bacteriology of the blood* has been frequently investigated with very contradictory results. That tubercle bacilli occur in the blood cannot be questioned and some recent work would seem to prove that more exact methods will yield more positive results. Inoscopy (Jousset) and the use of leeches (Gary) seem to aid materially in the search. The positive results obtained for other organisms are more numerous, but many have been questioned. Faulty technique would no doubt account for

some, but there remain a number of cases in which other organisms have been recovered.

Circulation.—The Pulse.—The frequency and tension are early and often permanently changed. The size of the pulse, its fulness and regularity, bear less definite relation to the pulmonary disease than the frequency and tension, and often until the late stages are only slightly, if at all, abnormal. The radial pulse is said to be influenced by the position of the arm on the affected side when contraction of the apex has occurred.

Frequency.—The pulmonary patient borders constantly upon the verge of excitement, and the visit of the physician or a call at his office will often increase the pulse twenty beats a minute. The best record is that taken at the patient's home by a nurse to whom he is accustomed. This instability of the pulse has some connection with the decrease of blood-pressure and a paresis of the vessels. Altitude increases the pulse-rate somewhat, which may decrease in a short time or persist.

The majority of all patients have at first a slightly increased rate (90 to 100), even when apyretic, and frequently when at rest in bed. The pulse-rate and temperature may be independent, but more usually there is a rather close connection between the two, which some have tried to express by allowing ten beats for each degree of fever. An increase above this rate, they think, is due to cardiac weakness. Forced feeding may produce slight acceleration of the pulse for a time. In some cases the pulse shows increased rapidity for short periods, but this is rather unusual, as when it once becomes rapid it usually remains so for some time. Mental excitement, slight physical exercise, attacks of coughing, and a full meal have a strong tendency to increase the rate in early as well as in advanced cases. In the latter, however, the pulse tends to be constantly rapid, and, varying somewhat with the temperature, increases slightly every afternoon. The range is usually between 88 and 120. This tachycardia is seldom noticed by the patient. Often as he improves and after the temperature has become normal the pulse-rate gradually decreases, but it may quickly fall to normal and remain so. Slight tachycardia may persist in healed pulmonary tuberculosis.

The *cause* of the increased frequency is still unsettled. It has been attributed to pressure upon the vagus by enlarged tracheobronchial lymph nodes, an explanation which certainly does not suffice in many cases. Brehmer thought the underdevelopment of the heart and the overdevelopment of the lungs were important factors. Another view is that it is due to the increased work thrown upon the heart by a narrowing of the lumen of the pulmonary vessels, or to a narrowing of the air passages, which Marié found diminished the number of respirations and accelerated the heart. A neuritis of the vagus, the fall in blood pressure, irritation of the sympathetic, increased irritability of the cardiac ganglia or muscles fibers, myocarditis, anemia, and dyspepsia have all been suggested as factors. The most probable cause, especially in incipient stages, is a weakening of the cardiac muscle and its nervous control due to the tuberculous poison. Valvular disease of the heart in pulmonary tuberculosis exerts little influence upon the pulse-rate.

Blood-pressure.—In many cases this is lowered from the very outset, and some have held that hypotension is present in the predisposed. It is held by many to be due to tuberculous poison such as tuberculin, which undoubtedly lowers tension (Teissier). As the disease advances and pronounced constitutional symptoms occur, the blood pressure becomes less and 90 mm. of Hg. (Riva-Rocci manometer, with 9 in. cuff) is not uncommon. A much greater variation exists between the blood-pressure in a reclining and in an upright position than in health.

Heart.—The heart may show little change throughout the entire course. It has long been held that it is reduced in size, and upon this Brehmer founded one part of his plan of treatment, graded walks. More recent observations have shown that hypertrophy is only a little less frequent than atrophy, which usually occurs only in cachectic patients. Many complications produce an hypertrophy, so that it is difficult to draw any conclusions at autopsy in regard to the heart early in the disease. The orthodiagraph has, it seems, shown a slight atrophy in incipient and hypertrophy or dilatation in far-advanced stages.

Displacement of the heart usually occurs gradually, but in some patients transposition to the right side seems to take place within a few days. The shrinking of the right lung frequently increases the area of pulsation and may so diplace the heart that the pulsation is limited entirely to the right side, extending in some cases beyond the mid-clavicular line. Retraction of the left lung may cause cardiac symptoms varying from slight discomfort to pseudo-anginal attacks.

Murmurs are not uncommon either at the apex or base, but in the writer's experience are more frequent at the apex and usually systolic. Some occur in patients in whom anemia can be excluded, where the displacement of the heart, if any, is slight, and where we are led to explain the murmur as due to pressure upon the great vessels. These patients show no cardiac hypertrophy. In a few patients murmurs occur in the interscapular region. Consolidation may transmit these murmurs widely. A cavity near the heart may alter the sounds, and murmurs synchronous with the systole are not infrequent in these cases. Murmurs are at times produced in cavities by the systolic distension of a large vessel or of an aneurism.

Acute dilatation of the right ventricle occurs far less frequently in tuberculosis than in other pulmonary diseases. Dilatation of the right side of the heart in advanced stages is, however, more frequent than many observers have held. In many chronic cases, where the intrapulmonary vessels are either obliterared or reduced in size, accentuation of the second pulmonic sound occurs and the shock is at times easily palpable. Over the second left intercostal space the second sound is at times reduplicated (best heard when the patient reclines). A weakened first sound is rather frequent in well-advanced stages, and is often more pronounced during acute attacks.

Palpitation.—This in neurotic subjects is usually a venous phenomenon associated with hypotension. The slighter forms are frequent and few patients entirely escape them. The severe forms occur occasionally after too vigorous exercise, and are most likely to be met with in advanced

stages. They are more frequent at puberty and at the menopause, sometimes precede hemoptysis and accompany dyspepsia. Some have noted pain in the neck along the vagus. Cardiac distress, due at times to dislocation of the heart, may also be found in a few patients not suffering from palpitation.

Vessels.—Pulsation in the cervical vessels is of frequent occurrence. Temporary dilatation of the subclavian artery has been described by West, who thinks it not rare. Dilatation of the venules, possibly due to pleuritic adhesions, upon the upper thorax and about and above the costal margin is quite common. A murmur over the subclavian artery, first described by Stokes, is not unusual under the outer third of the clavicle, and has been held to be of diagnostic importance. It is more common on the left side and is rare in women. It may appear or increase during inspiration or expiration, and is due either to anemia or to compression of the vessel by a thickening of the pleura or by a muscle. The murmur is not constant, is usually soft and blowing, and the position of the arm or pressure by the stethoscope may increase or produce it. Œdema of the lower extremities is rare except in the very late stages, when it almost invariably indicates great cardiac weakness.

Cyanosis.—This may persist for years while the patient enjoys comparative health. In many it is more pronounced in the morning. In the late stages the lips and nails become blue and the face and extremities are often cyanotic. In early stages it seldom occurs except as the result of severe pleurisy or cardiac complications.

Skin.—The skin undergoes changes produced by malnutrition. In many patients in early stages, especially those undergoing treatment, the skin is clear, ruddy, and normal in every particular. The chilliness and undue sensitiveness to cold are less frequent now than formerly. In the majority some pallor of the skin is present and often the vessels are well seen through the "skim-milk" complexion (tuberculous diathesis). In some the skin is dull and opaque and the complexion muddy (scrofulous diathesis). In late stages the skin is often dry and harsh, and even furfuraceous (pityriasis tabescentium). The sebaceous as well as the sweat glands may be stimulated and the skin become oily. A pungent odor from the sweat is often noticed.

Pigmentation occurs rather infrequently and may consist in a general bronzing of the skin, less marked than in Addison's disease, or in a patchy, light yellow to pale brown, often shiny pigmentation, which may occur on the face or trunk, the so-called chloasma phthisicorum. A connection between intestinal disorders or change in the spleen and lymph glands has been suggested as the cause of this, which is said to be more common when the peritoneum is involved. Icterus is rare. An erythema is occasionally present, and, while usually accidental, may at times be due to a tuberculous poison. It occurs in connection with acute conditions and adenitis, and in some appears only when the fever is at a maximum. It may closely resemble the rash of scarlet fever, but usually spares the mucous membranes. Petechiæ rarely occur. Purpura may occur and some think it is occasionally due to the tuberculous poisons. Œdema of the skin rarely occurs except in complications or late in the disease.

The hectic flush in late stages or a reddening of one cheek and ear in moderately advanced patients is common. Subcutaneous emphysema, with crackling on palpation, due to a rupture of the lung, is a rare complication. Local tubercle may develop on the hand. Herpes labialis occurs periodically with slight gastric disturbances in some patients, and is not uncommon after a tuberculin reaction.

Hyperesthesia of the skin is common and is often elicited on percussion. It is said to spread or contract with the advancement or retrogression of the disease, and to be more acute when the temperature is elevated. In lesions of the upper lobe it is most frequently present in the supraspinous fossa.

Hair.—The nutrition of the hair suffers especially during fever. It often becomes dry and lanky, and may split. The hair may come out in considerable quantities, but the alopecia is seldom patchy, partial, or complete. In children and young persons the body is sometimes covered with a growth of fine, downy hair (Kidd).

Nails.—The down-curving of the nails may occur without, although usually with, clubbing of the fingers (Hippocratic digits), and is thought to be due to the loss of fat on the palmar surface and malnutrition of the matrix, as well as circulatory disturbances. The ridges and furrows which occasionally occur are due also to poor nutrition.

Alimentary System.—Symptoms referable to the alimentary tract are present sooner or later in nearly every patient, and while not as frequent as symptoms referable to the respiratory system, rank second.

Gums.—The gums in advanced cases, owing to the poor nutrition, are often spongy and soft, and pyorrhœa is not infrequent. A red line on the gums, is not peculiar to pulmonary tuberculosis. Its cause is undoubtedly a mild gingivitis. Bleeding of the gums is very common and caries of the teeth frequent, due possibly to the gingivitis.

Tongue.—This varies directly with the condition of the patient.

Tonsils.—The tonsils may be hypertrophied, but adenoid tissue is rarely present. Chronic granular pharyngitis is common. Stomatitis is infrequent in early cases, but aphthous ulcers occur at all stages. Thrush may occur on the soft and hard palate, tonsils, tip and root of the tongue and mucous membranes of the cheeks. Usually of slight importance, it may penetrate into the deeper vessels, cause thrombosis, and even produce cerebral metastasis.

Digestion.—The digestion may be good to the end and many patients recover without the slightest digestive disturbance. A majority, however, suffer at some time from digestive disorders (70 to 90 per cent.), and women more than men. The type of the disease seems to exert less influence than its acuteness. Patients who escape have usually been good eaters, and the appetite is the best guide to the digestion. Alcoholics and those who have abused their digestion pay usually heavy penalties. Distress or anorexia may occur while apparently all the gastric functions are normal, but on the whole the gastric tolerance is remarkable In many patients with gastric disturbance no pathological changes in the stomach, except possible slight hyperemia, have been found. Dyspepsia

when present usually becomes less marked as the pulmonary disease advances, and when it is arrested the dyspepsia generally subsides.

The gastric juice is normal in many early cases (50 per cent., Brieger), but as the disease advances it is frequently abnormal, and in severe cases over 80 per cent. show some change. Hyperacidity may be present in early stages, while later subacidity is more common. The secretion of HCl is independent of the fever, but with other constituents of the gastric juice seems to be reduced in far-advanced stages. A deficiency of the digestive ferments may occur early which later is compensated by more digestive fluids of an inferior quality (Hay).

The motor functions of the stomach usually run parallel with the condition of the muscles in general, and accordingly the motility may be deficient in advanced but also in some early cases. With loss of motility dilatation of the stomach occurs.

The rapidity of absorption is little changed at first, but with dilatation and loss of motility it is much diminished. Gastroptosis in these cases is occasionally present.

The *gastric disorders* have been well studied by Marfan. The appetite usually fails and after meals some distress is noticed, varying from slight distension to actual pain or cramps. Eructations are not uncommon, but pyrosis is infrequent. In some cases eating is followed by cough and cough by vomiting without nausea. This occurs more frequently after the evening meal, as the morning cough has in most cases completely cleared the air passages. The vomitus in these cases usually consists of undigested food. A peculiarity of the vomiting thus produced is the fact that the patient is often able and willing to eat again at once. This vomiting is due to the increased abdominal pressure during (a fit of) coughing and possibly lessened tone of the musculature at the cardiac orifice. The cough is caused by rapid absorption of the fluid and increased secretion in the lungs.

Anorexia.—When tissue hunger is greatest, wrote Dettweiler, the appetite is often least. Anorexia, however, is rarely complete in the earlier stages unless profound constitutional symptoms are present. Many patients complain of no appetite, but eat, and eat well, and these are less liable to digestive disturbances. Again, many patients are hungry until they see the food or until a few mouthfuls are taken, then appetite may be replaced by nausea. The appetite is frequently capricious, good for one meal and lacking for several, or good one day and lacking for several, but on the whole it diminishes as the disease progresses. The tastes may undergo striking changes, and food once relished becomes repugnant and strange or bizarre articles of diet are craved. An antipathy to fats exists in some patients. Desire for food is at times closely connected with the temperature, and at noon or evening, whenever the maximum temperature occurs, the appetite is poor or lacking. This is not always the case, as many patients with high fever eat well.

Pain.—Slight gastralgia often fleeting is frequent in early as well as in late stages. In others the pain occurs regularly either immediately after eating or later, and is rarely the only symptom present. Distension is a frequent cause. Pain in the epigastrium, immediately after eating,

may occur when the stomach is normal and ulceration is present in the tranverse colon.

Nausea.—Nausea is very common at all stages. It may occur for some time before the physical signs are sufficiently pronounced for diagnosis. In the terminal stages it is often present and accompanied by vomiting. Many times it is manifested only in the morning, and may prove most stubborn. Again, it comes on when after one or two mouthfuls the appetite vanishes and the patient tries to force down a little more food. It often occurs without vomiting, and may cause much distress.

Vomiting.—This may occur with or without nausea. Without nausea it is usually due to violent paroxysms of cough and is more frequent in basal lesions or when a change of posture is made, generally on arising. One patient with a large cavity in the upper lobe vomited every morning and never expectorated at any time. Vomiting after nausea or other gastric symptoms is less frequent, but far from uncommon, especially in the later stages. In the first case the patient is often able to eat again at once; in the second the thought of food is repugnant. Other causes of vomiting are nervousness, pressure upon the vagus by bronchial glands, hyperesthesia of the posterior pharyngeal wall (sputum furnishing the necessary irritation), and nasopharyngeal catarrh. Vomiting may precede all other symptoms and persist after the disease is arrested.

Intestinal.—Constipation is frequent, and is no doubt in part due to the milk diet, in part to lessened peristalsis, caused possibly by the weakened musculature. Whatever the cause, constipation, and at times obstipation, is most troublesome and needs careful attention. It may be present until death, notwithstanding severe intestinal ulceration.

Diarrhœa.—This may occur for months before a diagnosis is made. The swallowed sputum can in many cases set up a catarrhal enteritis, which is more marked by its chronicity than by the frequency or profuseness of the stools. This form is more frequent in women, but may be caused by sputum swallowed during sleep. The tuberculous poisons may cause diarrhœa by irritation of the sympathetic system and increased peristalsis, by catarrhal enteritis, or by superficial erosions (catarrhal ulcers). This would no doubt explain the diarrhœa which in rare cases follows tuberculin.

Many tuberculous patients have diarrhœa from apparently trifling causes. In some, milk or raw eggs will in the course of time produce a pronounced griping and diarrhœa. A chilling of the abdomen and slight indiscretion in diet are sufficient in others. The cough and expectoration may diminish when the diarrhœa increases.

The liver and spleen are seldom affected.

The Genito-urinary System.—The genito-urinary organs present few symptoms in uncomplicated pulmonary tuberculosis.

The Urine.[1]—This is usually normal in every particular in the early stages. The liberal milk diet no doubt often accounts for the increased amount, but a true polyuria can occur. Some oliguria may be present

[1] See Clemens in Ott's *Chemical Pathology of Tuberculosis.*

in far-advanced cases. A decrease in the solid residue occurs in advanced stages and may fall below 30 gm. when cachexia sets in. The urinary salts vary with the temperature and the stage of the disease. The chlorides may decrease in exacerbations or when profuse expectoration occurs, but are usually normal.

Phosphaturia is held by some to be an early indication of pulmonary tuberculosis. Calcium phosphate predominates and increases as the emaciation progresses. Both calcium and magnesium increase at first and later decrease. Phenol has been found in the urine, especially just before death. Indican occurs more frequently, especially in children, than in health. The urea varies in amount, frequently normal at first and often decreasing late in the disease; it varies with the diet, exercise, and temperature. Acetone, sugar (without diabetes), peptone, and albumose have been found. Albuminuria is rare in early and is usually met with only in far-advanced stages. Teissier has described an intermittent form occurring in young individuals with a family history of pulmonary tuberculosis. An orthostatic form has been described. The diazo reaction or some of its modifications occurs inconstantly in some patients in advanced stages.

In 656 patients at the Phipps Institute, Philadelphia, for the most part in a far-advanced stage, sugar was present in 13, albumin in 153. Casts were noted in 37 and the diazo reaction in 60 among 495 cases. Poisonous substances, ptomains, have been found in the urine of patients with apparently normal kidneys and tubercle bacilli occur very occasionally without apparent renal disease. It is no proof that because injection of urine or its residue causes a "reaction" similar to that produced by tuberculin, that tuberculin is in the urine, for other substances may cause this reaction.

Inflammation and displacement of the uterus are caused by an aggravation of preëxisting trouble, and in some cases by cough.

Menstruation.[1]—This may be scanty or cease early in the disease, especially when the patient is anemic. Change of residence may also affect some patients. An onset at the time of puberty may delay menstruation for years. As the disease advances the menses usually, if not previously disturbed, become irregular and finally cease. With improvement menstruation begins again. In a few the menstrual function continues to the end. Menorrhagia occurs in a few cases, but rarely persists. In some cases the symptoms and physical signs are undoubtedly more pronounced at this time. The premenstrual fever occurring for about one week before menstruation is well recognized, while many hemoptyses occur and recur or the expectoration may be increased or present only during this period. Dyspnœa may also occur.

Pregnancy.—Pregnancy can occur in very advanced stages. During pregnancy the disease is often held in abeyance, to proceed more rapidly after parturition.

The Nervous System.—The nervous system is often early affected, and few patients entirely escape some nervous disturbance. This would

[1] See Macht in *American Journal of the Medical Sciences*, 1910, cxl, 835.

be expected in neurotic individuals, but while usually more pronounced it is by no means confined to them.

Psychical Changes.—An alteration in the disposition of the patient is not infrequent, but is in many cases only "apparent," as in a large number the real character is laid bare. By many all sham and pretension are thrown aside, perhaps unwittingly, and selfish traits, previously fostered by foolish parents, may become so pronounced that the patients try to exert despotic sway over all their associates and attendants. Fortunately, these examples are rather rare. On the other hand, some dispositions, naturally quiet and refined, seem as the disease advances to become so unselfish, so ethereal that they suggest another sphere in more ways than one. Chronic invalidism rarely leaves the character unchanged and treatment which constantly enforces self-consideration is not conducive to unselfishness. And yet years of institutional life and the constant solicitude of the family and friends affect singularly little the character of many chronic tuberculous patients.

Indecision, vacillation, and changeableness are frequent characteristics in some patients. Their judgment of men and affairs, their plans and outlooks, often change from day to day, or may be entirely reversed. Forced inactivity produces lack of concentration in some. The mental faculties are generally well preserved to the end and, in fact, may become more acute and out of all proportion to the bodily strength. The patient may plan and attempt to put into execution at once many schemes consigned to failure at the outset, little realizing the effect upon his jaded body. In a few, ideas of self-importance and of grandeur, great nervous irritability, suspicion and susceptibility to suggestion, are marked.

This, however, is not a true picture of the ordinary tuberculous patient. The vast majority, though depressed at first, soon rebound and improve or fail, they remain the same men and women they were before they became sick. The *spes phthisica* is common and may be pronounced even to the end, but the vulgar opinion has been until recently so pessimistic that it is not impossible for the patient to escape its influence, and many arguments are necessary to convince him of the possibility of a "cure." He quickly recognizes the serious illness of a fellow-patient, and it seems impossible that he should not realize the gravity of his condition.

Neuroses.—Neurasthenia is more common in pulmonary tuberculosis than in any other disease. No doubt it has an organic basis in the poisoning of the higher centres, but, however that may be, few escape it. At first it may be so pronounced that it masks the tuberculosis, which may be overlooked for some time. In other cases it develops only when the patient is well on the road to recovery, and forms a serious complication. Physicians and nurses, when attacked, are peculiarly prone to this neurasthenia. Pressure in the head, giddiness, fear, anxiety, vasomotor disturbances, and especially sleeplessness are common. When pulmonary tuberculosis occurs in neurasthenia or hysteria the nervous symptoms are usually increased. Hysteria occurs much less frequently and most often just before or during the menstrual period. It tends to disappear

with the progress of the pulmonary disease, and is rarely seen in men. Aphonia is not uncommon, but convulsions or spasms are rare.

Psychoses.—Psychoses are very much rarer in pulmonary tuberculosis than pulmonary tuberculosis in psychoses. Two classes may be recognized: "First, a group peculiar to the disease itself; second, a group including the usual types of insanity determined by a lowering of nutrition" (McCarthy). In the first class are patients with no hope of recovery, but happy and contented and often with a decided grade of unreason. They closely simulate paresis. This type differs from the form described by Clouston, in which depression advances to melancholia, and morbid suspicion, marked loss of memory, a desire to be alone, irritability, and delusions of persecution occur.

The second group includes melancholia, mania, dementia præcox, hysterical insanity, and delusional insanity. Melancholia develops early, rarely late in the disease, but mania is rare. Suicidal tendencies are not uncommon in these. The age incidence of pulmonary tuberculosis is the same as that of dementia præcox, and the association of the two diseases may be thus explained.

Tremors are common and usually occur on voluntary effort. The reflexes are often exaggerated, but may be decreased or absent, especially in marked asthenia. The knee-jerk is increased in one-half of the early cases. The ulnar reflex is held by McCarthy to be very suggestive of pulmonary tuberculosis, and may occur only on the affected side. This author has also found Chvostek's phenomenon present in 16 out of 287 cases of pulmonary tuberculosis. These phenomena depend upon the hyperirritability of the peripheral neuronic system.

Neuritis.—The peripheral nerves are seldom affected, and sensory are much more frequent than motor disturbances. The lesion can be limited to a single nerve, a plexus, or involve all the peripheral nerves. The leg is usually more affected than the arm, and the external perineal nerve may be the first affected. Atrophy of the affected muscles occurs, but usually a few are spared in an extremity, and so some motion is preserved. Paresthesia often precedes this type. Sensory neuritis may affect the skin, muscles, periosteum, and joints, or an entire extremity (acroparesthesia). Neuralgia of the intercostal nerves, the trigeminus, of the sciatic, and other nerves are common. Arthralgia, melalgia, myalgia, and dermalgia all occur.

Pressure neuritis may occur in the vagus, due to enlarged bronchial glands, and is manifested by rapid pulse, cough, dyspnœa, hoarseness, and laryngeal spasm or paralysis. Pressure on the sympathetic by retraction or thickening of the pleura may, by its cervical and brachial connections, cause a dilatation or contraction of the pupil or neuralgia in the arm. Dilatation of the pupil may occur before the pulmonary symptoms are manifested. Pressure of glands upon the recurrent laryngeal nerve may cause hoarseness.

Pulmonary disease can cause, as Head has shown, referred pains, irritative phenomena, hyperalgesia and neuralgia, in the skin of the neck and thorax by the connections of the sympathetic and vagus. Some have tried to connect the hyperalgesia with the location of disease and

others have proved that muscle spasm first and then atrophy occur in the muscles of the thorax (Pottenger). Connection with the trigeminal nerve may cause pain in the forehead, eyes, and head. The neuralgic pain may occur suddenly, dart from front to back, is little affected by ordinary breathing, but may be by deep respiration. Pressure lessens the pain, which is most frequent in the initial stages.

The vasomotor nerve supply is very unstable, and limited redness of the skin, especially of one cheek on the affected side or of both cheeks, elevated temperature in limited areas, localized asphyxia, sweating and ecchymosis, and a syndrome closely simulating exophthalmic goitre, are all probably the result. Myoidema is probably a functional nervous derangement of the muscles. Hoarseness, especially the premonitory type, depending upon a weakness of the adductors, is due also to the same cause.

Sexual desire is held by many to be increased, but this is in all probability due rather to the fact that pulmonary tuberculosis usually attacks young adults in the prime of life, and that the treatment consists of abundant feeding, enforced rest, and lack of occupation.

Herpes zoster, due to changes in the posterior root ganglion, is not rare. It is most frequent in the ninth to the twelfth dorsal segments, but occurs on the face, and in one patient extended over the right leg as low as the knee. The discomfort is often slight, but the pain may be very severe. There seems to be no connection between the pulmonary lesion and the side affected. In some cases the hemorrhagic variety occurs.

Headache is of frequent occurrence (in about 10 per cent., Cathala), and is often stubborn, hard to control, and bears no relation to the extent or stage of the tuberculosis. It is rarely so severe that sleep is lost. It is frequently due to overuse of the eyes with poor muscle balance or weakened musculature, but is said to occur from functional disturbances as well as from organic lesions.

Sleep.—Insomnia is not infrequent. Change from an active to a quiet life, indigestion, cough, fever, sweats, and more rarely pleurisy may all contribute; but neurasthenia and nervousness are most frequently the cause. It often occurs periodically, and high altitudes in some cases greatly increase it.

Cough.—Frequency.—Cough is the most frequent and, as a rule, the most constant of all symptoms in pulmonary tuberculosis. It usually first draws attention to the lungs, but a slight cough may exist for months and attract little notice. In rare cases cough is absent throughout, and not very infrequently a patient is seen with a well-marked cavity whose cough has passed entirely unnoticed.

Other things being equal, the cough varies in frequency with the amount and character of the expectoration, but no direct relation exists between the gravity of the disease and the severity of the cough. It depends to a considerable extent, however, upon the nervous excitability of the patient and the part affected. The mucosa of the respiratory tract is not equally sensitive throughout, and is most irritable in the posterior interarytenoid space and at the bifurcation of the trachea. The irritability decreases downward, but an irritation once begun may rapidly

increase and spread to parts showing previously slight susceptibility. The pulmonary tissue has little or no sensitiveness. It is probable that when the primary focus is situated near one of the main bronchi which becomes involved early the cough is more severe. In some instances the patient can select a definite point on one side as the origin of irritation causing cough. Cough and expectoration may both increase during the menstrual period, and youth as well as fever seem to increase the cough. An acute pleurisy rarely causes and frequently checks cough, but a chronic pleuritic irritation may produce a dry, hacking cough.

Varieties and Cause.—Cough in the majority of cases is at first short, dry, hacking, not hard, and rather frequent. It may occur throughout the day or more frequently be limited to the early morning hours or night. As the disease progresses the cough becomes looser, productive, and in many cases more frequent, especially when softening is taking place. In patients with a catarrhal onset the cough is frequently loose from the onset. The character varies with the amount of secretion and the part of the respiratory tract affected. Before the bronchi are affected the cough is usually dry, short, and hacking; after they are affected the cough is similar to that in simple bronchitis. Cough may be divided into dry and moist or productive. A dry cough may be due to irritation of the respiratory tract or to a reflex.

The *productive cough* is caused by the irritation of the mucosa, usually by the slowly or rapidly collecting secretions. The morning cough is usually the result of the irritation of the sputum slowly gathered during the night. Change of position and sudden contact of the secretions with other parts of the mucosa no doubt play some part. This is true in many cases with cavity, where either a change in position or an overflowing of the cavity causes continuous cough until the vomica is emptied.

The explanation of the cough frequent with many patients *on retiring* is more difficult. Sudden contact of the secretions with parts of the respiratory mucosa hitherto for a time free, impact of air on parts of the larynx previously protected, congestion of the larynx due to the position of the head, hyperemia of the internal organs due to contraction of the peripheral vessels from the contact of the skin with the cold sheets, increased difficulty of expectoration, hyperemia, and consequent increased irritability of the respiratory centre (which is lessened during sleep) have all been offered as explanations.

In a few patients cough continues to be noticed *after meals*, especially after breakfast, when it has ceased at all other times. This is due chiefly to the hot fluids taken with the meal, but increased cough may occur from food by irritation of the upper respiratory tract, rendered more sensitive from inflammation or ulceration, either by direct contact with the food or by the movements of the œsophagus or pharynx, by direct pressure upon the trachea or bronchi by enlarged glands as masses of food pass by them, by the temperature of the food, by the pressure of the distended stomach upon the diaphragm, or by the inhalation of steam from warm drinks. Increased frequency or depth of respiration as in laughing, singing, rapid talking, fast walking, may all cause cough.

Paroxysmal cough may be due to the emptying of large cavities, to ulceration at the tracheal bifurcation, or to irritation by enlarged bronchial or mediastinal glands. The respiratory efforts are not so close together, but fully as prolonged and as exhausting as in whooping cough.

The *emetic cough* is common in advanced stages. It is most frequent in the morning, but may occur after each meal and lead to rapid emaciation. The cough causing the vomiting may be dry.

Nervous cough is often continuous and irresistible, without any intervals between the paroxysms. It usually increases suddenly and often is absent at night, and can last for months with little effect upon the general health. It is dry and high-pitched, and is frequently replaced by other nervous symptoms.

The untoward results of cough are numerous and in some instances serious. Involuntary passage of the urine is not uncommon in women, but involuntary discharge of the feces is rare unless the sphincter is weakened. Dyspnœa and cyanosis are frequent and emphysema may occur. Pneumothorax and subcutaneous emphysema are both in part the result of cough. Pain in the chest from excessive cough is common and the abdominal wall may become very tender. The excessive exercise from coughing may completely exhaust the patient and produce profuse sweats. Hemoptysis due to increased blood-pressure may be traced to cough as well as cerebral congestion and hemorrhage. Hernia, displacement of the uterus, and even abortion may be caused by it. Aspiration of a fluid sputum into healthy bronchi may take place during paroxysmal cough. Tachycardia due to severe coughing is more frequent in early than in late stages.

Expectoration.—Few symptoms are more troublesome than this. It is closely associated with cough, and many patients cough simply because they must expectorate. In a few cases from the outset and in many only after much training will the patient allow the sputum to collect just below or in the larynx, when by clearing the throat it can be raised. Bronchorrhœa is sometimes a distressing symptom, and the patient may be forced to spit day and night. The rales in the trachea may prove very annoying, especially when the patient retires. These often persist, and in fact may be accentuated as progress is made toward recovery. In a few cases slight expectoration may be the only symptom, and it is not rare to have attention called by hemoptysis to a small quantity of sputum in the morning which, on examination, is found to contain tubercle bacilli. As the disease becomes arrested the sputum may be the only symptom remaining, and it may persist for months or even years, and after the disappearance of tubercle bacilli. Destruction of the cords (true and false) renders expectoration much more difficult. If the amount of expectoration is out of proportion to the strength the condition is grave, and when weakness is pronounced it is impossible for the patient to raise the sputum. The relation of the extent of physical signs to the amount of sputum is very uncertain, for patients with slight signs may have profuse expectoration, and *vice versa*. Patients with moderately coarse "moist" rales over an entire chest may be entirely free from expectoration, due either to the fact that the rales are pleuritic in origin

or to absorption of the secretions in the lungs. The latter can hardly take place when the sputum contains tubercle bacilli.

Respiration.—This is usually quickened and rarely falls below 20 or exceeds during rest 30 per minute, except with an acute exacerbation or in far-advanced stages. It is astonishing to see the amount of pulmonary involvement present without dyspnœa except on overexertion, although marked dyspnœa may be present without physical signs.

The majority of all patients, however, are short of breath on exertion, and a rate of 95 per minute has been recorded (Damaschino). Later in the disease, emotion or exertion may produce violent dyspnœa, but orthopnœa is very rare. Patients with a nervous temperament usually have more rapid respiration, and with previous emphysema the dyspnœa is usually greater. Oppression in the chest may be present without dyspnœa.

The cause is most frequently mechanical, and is due to the involvement of lung tissue and the lessening of the complemental air space. An obliterative pleuritis, or a tracheobronchial adenopathy, may produce marked dyspnœa. Serous effusion, accumulating very gradually, and, in a few cases, pneumothorax, cause no respiratory distress. Aspiration of secretions into the air passages may cause pronounced dyspnœa. Dyspnœa seems to be due less to the extent than to the rapidity of the involvement, less to the stage than to the extent of the lesion, and is most pronounced in those cases in which miliary tuberculosis of the lungs supervenes upon a chronic process. Shortness of breath is influenced mechanically by food. In chronic forms, cardiac weakness, palpitation, or thickened pleura may cause pronounced dyspnœa.

Dyspnœa may be *toxic* in origin. With a rise in temperature the rate of respiration is usually increased and the depth diminished, but in many instances this is due to an increase in the pulmonary involvement. Anemia may be the cause in a few patients.

The relation of the respiration to the temperature and pulse is not constant. Cheyne-Stokes breathing is rarely seen except with meningitis. Biot's type of breathing occurs shortly before death.

Hemoptysis.—While often applied to a spitting of blood from any source, hemoptysis is here used to denote a spitting of blood which has escaped into the air passages below the larynx.

Frequency.—This may be said to be about 60 per cent. of all cases, but varies according to different authorities from 24 per cent. to 80 per cent. Age has a marked effect upon the frequency. It is rare before puberty, but a fatal case has been reported in an infant of ten months (Hoffnung). In old age hemoptysis is also uncommon, but probably more frequent than in infancy and childhood. Sex and age together seem to exert some influence on its frequency. A study of figures shows that while in males more hemoptysis occurs in the third decade, in females more occurs before twenty and after forty. It also shows that more males than females have hemoptysis, and that in males this symptom occurs more frequently in the years of greatest activity. There is apparently no connection between height and hemoptysis.

Hemoptysis is an accident which may occur in any form of pulmonary

tuberculosis, and is not a sufficient basis for classification. In the more acute varieties it is much less common, but occasionally ushers in an acute process engrafted upon a chronic form. Fowler has reported a fatal case occurring in acute miliary tuberculosis, and A. Fränkel one in pneumonic phthisis. Patients with a family history of tuberculosis seem very little more liable than those without this taint. It is unusual to find a patient who has had but one hemoptysis, and some patients, usually those semi-arrested, have a marked tendency to it. Many of them do well, and Andral reported a case in which hemoptysis occurred from the twentieth to the eightieth year. At autopsy numerous calcified tubercles were found in the lungs.

The connection between hemoptysis and physical signs is notoriously uncertain. It may be severe in patients without physical signs, but in these cases calcified tubercles about the lobes of the lung are frequently seen in the radiograph. A fatal case has been reported in a child in which the total area involved could be covered by the tip of the finger (Fowler). On the other hand, patients may have extensive ulceration and large cavities in both lungs without hemoptysis. In sanatoriums it has frequently been noticed that it is usual for several patients to have hemoptysis about the same time; an epidemic of hemoptysis.

Site and Pathology.—Small hemoptysis, bloody streaks in the sputum, can unquestionably come from the bronchi, but more blood than this comes almost invariably from the pulmonary vessels. Pink and rusty sputum may be due in many cases to diapedesis from the bronchial or pulmonary capillaries, and, while usually not serious, may prove fatal (Fowler). Such sputum, however, is most common after hemoptysis of larger amounts. Some hold that the lumen of the pulmonary vein (more rarely the artery) in some early cases is narrowed by a tubercle in its walls, and that there is a consequent rise of blood-pressure, especially at this point, where the rupture occurs. Fatal hemoptysis from ulceration of a vessel wall without the formation of an aneurism is exceedingly rare.

These aneurisms are nearly always found on a middle-sized branch of the pulmonary artery, rarely on the pulmonary vein, and then early in the disease, and more rarely on the bronchial artery. The larger vessels, owing to more elastic tissue, resist erosions, at least until thrombosed. The aneurisms are globular, rarely fusiform, and occur generally upon the unsupported side of a vessel in the wall of a small cavity, which they may fill. Their size, usually that of a large pea or small cherry, seldom exceeds that of a small walnut, and, while frequently single, they may occur in numbers. Aneurisms may be found in the walls of the bronchus. They are most frequent in the middle area of the lung, near the periphery, *i. e.*, the lower part of the upper lobe (more common) or the upper part of the lower lobe, where the pulmonary movement in respiration is greatest (West). The rupture usually occurs at the distal boundary of the dilatation.

Amount of Blood.—The amount of blood varies from the slightest trace to several liters, but is usually less than ½ ounce (15 cc.). The blood, usually frothy, may be coughed up by mouthfuls every few minutes for days, or it may come up in a gush and pour out of the mouth and nose

and large quantities enter the stomach. In some cases the blood slowly collects in a cavity, finally overflows, irritates the mucous membrane, and is then coughed up. In rare instances with large excavation the patient may die from hemorrhage into the cavity, with little or no hemoptysis. Hemoptyses seldom occur singly, and generally two to four follow each other in the course of five or six days. The sputum is almost invariably blood-stained for several days afterward.

For clinical purposes it is sufficient to classify hemoptysis as streaky, slight (more than streaks and less than 30 cc.), moderate (30 to 100 cc.), severe or copious (100 to 250 cc.), and profuse (over 250 cc.). These amounts refer to the quantity of blood lost in twenty-four hours. In 50 per cent. of all cases the hemoptysis is streaky, in 15 per cent. moderate, and in 10 per cent. severe and profuse. As 25 per cent. of all patients have no hemoptysis, it is an urgent symptom in about 10 per cent. (West).

The blood varies in color from bright red to very dark, depending more upon the time it has remained in the lung than upon its origin. In any case bright red blood cannot be said positively to come from a vein, as the bronchial arteries contain such blood. The blood is rarely clotted at first, although in some instances no fresh blood is ever raised. As the hemoptysis ceases clots are more frequent, and in some cases casts of the bronchi are expectorated. The expectorated blood usually clots quickly and is alkaline. Ortal has found that the blood in some cases possesses the power to agglutinate tubercle bacilli. The bacillary contents of the blood vary considerably, but it often contains tubercle bacilli, and in a "primary" hemoptysis should be carefully examined.

The *causes* may be divided into intrinsic and extrinsic. The former, the underlying factors in every case, have to do with the pathological changes in the vessel wall. Hemoptysis other than capillary never occurs unless the vessel walls are weakened by disease. In some cases the vessels seem to be hereditarily weak, and these patients may suffer from frequent hemoptysis. Extension of the disease process into the vessel wall usually occurs in the lung, but diseased glands may ulcerate into a vessel and expulsion of lung stones or fibrinous casts seems in some instances to be connected with hemoptysis.

The systemic blood pressure is much lowered in most cases of advanced pulmonary tuberculosis, but the pressure in the pulmonic system is in many advanced cases apparently raised and an accentuation of the second pulmonic sound is frequent. The frequency of the pulse is often in inverted relation to the arterial pressure. In advanced stages the diminished volume of blood reduces the frequency of hemoptysis. In the majority some rapid increase of blood pressure is held necessary for its production. This is generally thought to be afforded by some extrinsic cause, such as violent exertion, particularly of the arms and thorax, or violent respiratory and general exertion, such as is entailed in mountain climbing. It is a singular thing, however, how rarely hemoptysis follows immediately on any single act of overexertion, and a large percentage (nearly 80 per cent.) cannot be connected with overexertion. Hemoptysis can be divided into two classes: in one it

seems to be an accident in the course of the disease, and in the other it is simply one of the symptoms of an acute exacerbation.

Hemoptysis occurs frequently in the early morning hours, a time when the blood-pressure in the pulmonary system is subject to marked variations. Some, however, can be traced to prolonged overexertion, but occur many hours later (twenty-four to seventy-two). Emotion stands in a somewhat similar relation.

An attempt has been made to connect hemoptysis with barometric changes, wind, moisture, precipitation, sunshine, and cloudiness, and combinations and quick variations of them; but this has so far failed. It is more frequent (Gabrilowitsch) during the spring and fall, and the sudden thermometric and barometric changes have been adduced as the causative factor. High elevations are said to have no effect upon its occurrence, but patients who exercise immoderately on arrival are more liable to it than in lower elevations. Suppression of blood, either from hemorrhoids or from menstruation, has been held as a cause. However it may be, hemoptysis frequently occurs in women about the menstrual period, and some patients have slight hemoptyses every month over long periods. These often have little effect upon the general health, and cease usually when the disease is fully arrested. Coitus may cause hemoptysis (Plique). Irritant gases may be a cause, and one case was observed in which small hemoptyses occurred twice after the administration of ether. Flick, Ravenel, and Irwin have drawn attention to the frequency of the pneumococcus in the blood of hemoptysis and in the sputum of many patients who suffer from it.

The immediate *effect* of hemoptysis depends upon the quantity of blood lost, the amount of fundamental disease, and the complications. The effect on the ultimate termination is very variable, and no matter how severe or how slight hemoptysis has been, it is well to give a guarded prognosis. A slight hemoptysis may be the precursor of a severe and fatal bleeding from the lungs, but as a rule the earlier the stage the less serious the prognosis, which after twenty-four to forty-eight hours is more favorable, as by this time a thrombus can form. In a few cases hemoptysis is followed by some improvement—fall of temperature and loss of feeling of oppression; often this is only temporary. Heart action which produces high blood pressure and consequent hemoptysis is also favorable to healing. An initial hemoptysis is often of advantage to a headstrong patient who, thoroughly frightened, is willing at once to take all precautions. For this reason it is wise not to pass over an initial hemoptysis lightly.

In a much larger proportion, hemoptysis seems to exert no effect upon the immediate course and appears to be simply an accident. Except a few days' rest in bed it entails no discomfort upon the patient.

In some it has to be considered as simply one of the symptoms of a progressive lesion, with accompanying dyspnœa, rapid pulse, and elevated temperature. In this case the most usual occurrence is an attack of tuberculous bronchopneumonia of more or less severity. Aspiration of the blood into a whole lobe is rare and affects the lower lobes more frequently. The resulting pneumonia may be due to the secondary organisms, and run a more or less atypical course, or to the tubercle bacilli,

when the result is much more serious. The fear and consequent behavior (great agitation and refusal to follow advice) of some patients seem to have a marked influence upon the frequency of this complication, although the amount of blood is also of importance.

It is not unusual after hemoptysis to have great dyspnœa, rapid pulse, high temperature, cyanosis, and death in a few weeks from acute miliary tuberculosis of the lungs. In fact, any bleeding followed by one of these four symptoms is to be looked upon as serious, and an absence of these indicates that little immediate fear need be entertained. Slight fever usually occurs for a day or two, due no doubt to the absorption of exuded blood. Profound prostration may follow the loss of a slight amount of blood when no physical signs are to be detected. A profuse hemoptysis may turn the tide against the patient.

Death may result from loss of blood, either immediately or in a few days or weeks, and comprises about 2 per cent. of all deaths in pulmonary tuberculosis. According to Williams, fatal hemoptysis is nearly twice as frequent when softening begins and nearly five times as common when there is excavation. It is much more frequent in males, but apparently it exerts little influence upon the course of the disease in women but is more unfavorable in men. When bleeding takes place from a vessel on the side of a large cavity it may be fatal and hemoptysis slight or absent. In other cases the blood pours out so rapidly that death from suffocation follows, the common cause in fatal hemoptysis. Cerebral anemia and syncope are more common causes of death than exhaustion. Death from shock or acute anemia is of rare occurrence.

Hemorrhage from the lung can take place into the pleura, and some (Sticker, Dieulafoy, etc.) hold that spontaneous hematoma of the pleura is almost always the result of a preëxisting pulmonary tuberculosis.

Pain.—Few patients whose disease runs a more or less chronic course escape thoracic pain. Hérard and Aufrecht found it in two-thirds of their cases. In 1513 patients at the Phipps Institute, Philadelphia, 71 per cent. had some pain, including that referred to the extremities. It may be the first or the most pronounced throughout symptom.

The cause is very uncertain, and is said to be due to pleurisy, neuralgia, neuritis, myositis, nervous erethism, pulmonary congestion, pressure from enlarged glands, localized fatigue of the muscles used in respiration or in coughing, extension of inflammation to the intercostal nerves, contraction of old cavities, traction on pleural adhesions or on the heart, pneumothorax, tuberculosis of the rib, as well as to the intrapulmonary disease (the referred pain of Head).

Pain over the upper front is most frequently referred or due to acute pleurisy or to traction on pleural adhesions. Pain over the base of the lung is usually pleuritic, while pain in the interscapular area may be referred, due to pleurisy or to pressure from enlarged glands. Pleurisy is not always accompanied by pain, as the friction can at times be heard several feet from the patient and cause little or no discomfort, but pulmonary tuberculosis is practically always accompanied by pleurisy, and it is an exceedingly rare thing to find no pleural adhesions at autopsy.

Pleuritic pain may be severe or slight, may occur only after a deep inspiration, expiration, cough, sneeze, or yawn, or may be continuous and every breath be attended with pain. This pain varies from a vague discomfort, a sense of pressure or of tension, to a sharp, lancinating pain which cuts the breath short and produces sweats and great prostration. It may occur in any part of the chest, but is most frequent in the interscapular, subclavicular, and infra-axillary regions. The pain may be noticed upon the opposite side, in the epigastrium, the hypochondrium, the sacrum, the shoulder on the affected side, and even radiate down the arm (diaphragmatic pleurisy). Singultus is not frequent. Slight pleuritic pain is often accompanied by a short, hacking cough and fever. A sudden cessation of pain suggests fluid.

Patients often complain of pain that cannot definitely be said to be due to pleurisy, and in many cases is no doubt the referred pain of Head. The site varies, but it usually occurs on the affected side. The most common locations are the infraclavicular area to the third rib, the interscapular and the infra-axillary regions. Pain also occurs, but less frequently, at the apex, in the suprascapular and subscapular areas, and may radiate down the arm. Cases have occurred where angina pectoris was suspected from the localization of the pain. The character of the pain is very variable, being most frequently a slight feeling of discomfort, of localized fatigue, or soreness. It may be constant in location and time and last for days, months, or even years. It is most frequently fleeting, difficult in some cases to localize, and in others so variable in its location that the pain is thought to be "rheumatic." The pain in some instances escapes the patient's notice until a physical examination is made and percussion begun. In other instances deep pressure is necessary to elicit it, and again the skin may be so sensitive that the slightest touch causes severe pain, the clothes cause great discomfort, and the patient lies on the opposite side. In these cases of hyperesthesia the skin is often very sensitive to pressure between the fingers. At times the pain is described as going "through and through." In many cases the pain is independent of the respiratory movement, in others it is increased on any unusual respiratory movement, and is frequently noticed only on coughing, yawning, or sneezing.

Pain often precedes hemoptysis and may disappear on its occurrence. Intercostal neuritis with the classical points of tenderness is rare. An intercostal myositis has been described by Coplin and by Aufrecht. Louis attributed the pain in some instances to tubercles in the lungs, and Andral the pains which appeared with fever to the softening of tubercles, but the only pains connected with the pulmonary parenchyma are the referred pains of Head. Sokolowski, however, when stubborn pain, with poor general condition, chills and fever are present, believes a deep focus is extending toward the periphery of the lung. Severe pain from herpes zoster (before the eruption of the rash) or from pneumothorax (when many adhesions are present) may not be attributed to the proper cause for some days. Pain about the thorax, over the insertion of the diaphragm as well as in the abdominal and dorsal muscles due to cough, is not uncommon.

Voice.—Changes of the voice are of frequent occurrence. The slight "prodromal" hoarseness, often only temporary and fleeting, but recurring, may be the first indication of the pulmonary disease. The larynx may be perfectly normal. In advanced stages the voice often becomes weak, is easily fatigued, and on prolonged use may disappear. Excluding tuberculous laryngeal changes the cause of the hoarseness has been attributed to nervous conditions (one-third of cases, MacKenzie), neuritis of the laryngeal nerves, atrophy of this nerve (more commonly of the left, due to pressure upon it from pleural thickening, apical contraction, enlarged glands), laryngeal catarrh, or straining from severe cough, and collection of irritating sputum upon the cords.

THE PHYSICAL SIGNS OF PULMONARY TUBERCULOSIS

The chief importance of these relates to diagnosis. To a limited extent the physical signs vary with the time of day, especially in some advanced cases in which rales may be present only early in the day or heard only with the patient in the recumbent position. At the outset it should never be forgotten that extensive lesions, situated centrally, may produce only very slight or even no physical signs. Repeated examinations may be necessary to discover all the physical signs present at an early stage.

Inspection.—The patient, stripped to the waist, and covered with a chest cloth or blanket, should be placed in a warm room, either sitting (preferably on a revolving stool) or standing, so that a strong light falls diagonally across the chest, which should be viewed anteriorly, posteriorly, laterally, and from above.

Shape.—The general conformity of the chest varies from the normal to the most pronounced paralytic or phthinoid type. The shape seems to bear some relation to the stage of the disease and is a trifle long at first, with a slight prominence of the clavicle on the affected side. As the disease advances the chest becomes slightly smaller, due probably not only to emaciation, but also to change in bulk of the lungs. In unilateral disease the change in bulk of one lung may be compensated for by enlargement of the sound lung without any external manifestations.

The flattening of the chest so often seen in the late stages is in most cases more apparent than real, as can be easily observed by having the patient stand or sit erect and hold back his shoulders. In some instances this demonstrates a chest rounder and deeper than normal. The round chest with the falling forward of the shoulders often causes tilting of the scapulæ, the so-called "winged" scapulæ. The costal cartilages may be raised and the sternum depressed, forming in accentuated cases the "funnel" chest. The paralytic thorax is more often a result than a precursor of pulmonary tuberculosis, and may occur in other diseases. Changes due to intrapulmonary disease are most likely to be seen at the apex, those due to pleuritic disease at the base (except in children).

Asymmetry of the chest, absent only at first, is later often very marked and is best observed by comparing the clavicles. Shrinking below the clavicle is in part at least due to atrophy of the pectoral muscles. In

pronounced cases the shoulder on the affected side is lower. The pathogenesis of this atrophy is without doubt, Boix believes, analogous to that of arthropathic amyotrophy. Pottenger holds that it follows prolonged spasm. Bulging or undue prominence of the affected side may occur. Plate-like depressions or dimples in the inner first, second, and third intercostal spaces, due to old fibrous infiltrations or cavities, are not uncommon and the inspiratory movement of the anterior border of the right lung, when it has undergone compensatory enlargement, may be seen by a bulging of the left intercostal spaces for one-half to one inch from the sternum, while the rest of the side remains almost or quite motionless (Turban). Bulging of the interspaces otherwise occurs only when some complications arise. Tilting of the clavicle on the affected side has been described in early cases.

The area of visible cardiac impulse increases as the lung contracts and in some instances the point of maximum impulse may be found in the left anterior axillary line, in the right midclavicular line, or even under the angle of the left scapula (Kidd). Cavity and more rarely pleurisy produce such marked changes. A large area of cardiac impulse in the second, third, and fourth interspaces on the left usually indicates disease of the left apex. Displacement of the absolute cardiac dulness three-fourths or one inch to the right (to the middle of the sternum) is a typical symptom of right apical disease of some standing.

Movement.—Limitation occurs early, and a unilateral limitation or lagging may be one of the few signs present. In a majority of cases lessened movement occurs first in the subclavicular fossa, and can be readily seen from in front. In other instances the limited excursion can be observed more readily by standing behind the patient seated on a stool and placing the hands over the subclavicular fossæ. As the disease advances the limitation of movement is more marked, and in some cases, probably through the calcification of the cartilage, the chest moves only as a whole. Litten's phenomenon yields little information. Staining the chest yellow seems to aid in its observation. Local retraction of the chest may occur during inspiration, due probably to pleuritic changes.

It might be added that limitation of movement is due (1) to obstruction of the bronchi and deficient entry of air; (2) to change in elasticity of the lung through consolidation or fibrosis; (3) to pleuritic adhesions or pain; (4) to calcification of the costal cartilages; (5) to weakness.

Venous varices are of frequent occurrence near the costal margin usually equally upon the two sides. The subcutaneous veins over the upper chest may be dilated, often on one side, probably due to constriction of the intercostal veins through pleuritic inflammation and return of the blood through the anastomotic channels to the superficial vessels.

A *difference in the size of the pupils* occurs at times and the larger pupil is usually on the same side as the discoverable lesion, due no doubt to the pressure on or involvement of the cervical sympathetic system.

Mensuration.—The *circumference of the chest* is best measured in the plane of the junction of the fifth costal cartilage and the sternum. It should be taken during quiet respiration, at the postexpiratory pause, and after a deep inspiration and full expiration. Some confusion seems

to exist in regard to the terms "chest expansion" and "respiratory movement." The former should be used to indicate the difference between quiet respiration and full inspiration. The normal expansion in health is about $1\frac{3}{4}$ inches for males, $1\frac{1}{2}$ for females, the normal respiratory movement more than double these figures. Patients who have taken respiratory exercises, or who walk up graded paths, have larger measurements than those at rest, but both are in most cases below normal.

The *length of the chest* has been much discussed and in many far-advanced cases, especially those with a phthinoid or paralytic thorax, is considerably increased.

Chest Index.—This is the relation of the anteroposterior to the transverse diameter at the level of the junction of the fourth or fifth costal cartilage with the sternum. In health this may be stated to be 73, in early stages of the disease about 72, and in later stages about 76; it has no prognostic and little, if any, diagnostic value. There is some tendency for the chest to divide into two types, one flat (index 68 to 70) and one deep and round (index 78 to 80), but both slightly reduced in size and longer than normal.

Freund long ago called attention to the early calcification of the first costal cartilage, and more recently Gessner has attempted to measure the superior aperture of the thorax, applying here the laws governing the relation of the external to the internal pelvic dimensions. He finds "relatively often" a stenosis, more marked in the more acute types.

The lead-tape *cyrtometer* used in conjunction with accurate calipers will give a reliable outline of the chest, which recorded on paper can be used for comparison with future tracings. Many patients undergoing treatment show marked increase in size of the thorax. The pantograph, which produces an exact tracing of the shape of the chest in any size desired, is theoretically valuable, but practically of little use.

Spirometry has not proved of much value in diagnosis, as many early cases show little change in the tidal air; but used over an extended period may aid in the prognosis of an individual case. Hall has recently devised a method by which the vital capacity can be closely approximated. A sudden and marked reduction may indicate a new focus.

Pneumatometry.—Waldenburg's study of the inspiratory and expiratory forces seems to show that the inspiratory power is diminished even in incipient pulmonary tuberculosis, while the expiratory (except in extreme cases) remains normal. The reverse is true of asthma, emphysema, and bronchitis, but the diagnostic value is slight.

Palpation.—This combined with inspection affords the best means of determining unilaterally restricted movement. To palpate the apex it is best to stand behind the patient, and placing the thumb in the supraspinous and the fingers in the supraclavicular fossa, grasp the apex, so to speak, in the hand. The vocal fremitus is in many early cases little if at all changed from normal. In more advanced cases great discrepancy seems to exist at times between signs discoverable by palpation and signs obtained by other procedures. Vocal fremitus, for instance, may be either increased or absent over a cavity. Pleuritic friction and sonorous rhonchi are rarely palpable. Markedly increased vocal fremitus

usually indicates consolidation. Tussive fremitus may be of value in aphonia. Pottinger believes that by his "light-touch palpation" he can outline pneumonic areas in the lungs. Tenderness may be complained of on palpation, but is usually elicited on percussion.

Percussion.—Methods.—With the chest bare, the patient should stand or sit in a corner or near a wall, with his arms hanging loosely by his sides and his head straight. It is best to begin with immediate percussion of the clavicles. Often when percussing one side it is well to go from the resonant parts below to the suspected apex. In some cases the supraclavicular fossæ can be percussed more accurately from behind. If in doubt the part should always be percussed after a full inspiration, first from one side, then from the other. To percuss the axillary region properly the patient should either clasp his hands above his head or place them on the back of his neck and raise his elbows as far as possible. Percussion in women with lax or large mammæ should be done in the prone position.

Direct percussion in many instances is helpful, especially when comparing the note of the bases behind or the clavicles. Auscultatory percussion is of little value except in defining the limits of the lobes. Light percussion is best for superficial lesions; strong for lesions 5 cm. or more below the surface of the lung, which, however, even if extensive, may escape detection. When the involvement of pulmonary tissue necessary to produce any change in the percussion note is considered the absence of dulness in the incipient stage is not strange.

In some cases the first change in the percussion note is a shortening of the duration, although in many cases it is already accompanied by a rise in the pitch and a diminution of the loudness. Occasionally, emphysematous changes occur which mask the dulness even in some quite advanced cases. This change is no doubt the cause of the slight relative dulness at times detected on the apparently unaffected side.

In many cases on careful percussion a slight change in note is detected at the level of the second rib. If we percuss from below upward, at this level, the note becomes slightly higher in pitch and possibly a little shorter. This is not pathological, but is due to the increased thickness of the pectorals in these areas. Slight dulness may be found in the interscapular region (enlarged glands?) in some patients without any other abnormal physical signs ever occurring. Scoliosis or irregular configuration of the shoulder may cause slight dulness and apparent shrinking. Percussion over the vertebræ is not of much aid in apical dulness.

The dulness observed in incipient pulmonary tuberculosis is usually very slight, often requires much experience to detect it, and frequently increases as the patient recovers. In more advanced cases, and especially in those whose onset was with pleuritic effusion, the dulness may be very marked and pass even into flatness. Advanced tuberculosis may exist, however, with little or no change of note. Tympany or hyperresonance may occur when small foci compress the intervening tissue, when emphysematous changes have taken place, or with cavity or complications (pneumothorax). The cracked-pot sound may be heard more

frequently on the left side, over cavities with an elastic wall situated superficially in the upper anterior part of the upper lobes. It is nearly always, when pathological, associated with some degree of dulness, and is rarely obtained elsewhere than in the region between the clavicle and the fourth rib.

Increased resistance is associated with different degrees of dulness in many cases. Percussion in some instances elicits more or less tenderness, usually more marked on the side more affected. It is always advisable to determine by percussion the lower level of the lungs, as small areas of dulness in this region are readily overlooked. Lessened excursion of the diaphragm, which frequently occurs on the affected side, can be determined fairly accurately by percussion of the bases of the lungs at the end of full inspiration and expiration.

Krönig has suggested that the resonant areas above the clavicles be mapped out and these areas compared. A slight change in position is of little consequence, but a difference in size or in the sharpness of their definition is suggestive of disease. Very light and moderate percussion should be employed alternately in mapping them out. It is well to begin on the clavicle and along the border of the trapezius muscle and then to connect these points. Other methods have been suggested, but are not so simple as this.

Auscultation.—The first abnormal physical signs in pulmonary tuberculosis are those detected by auscultation, but even these may first occur months after the primary infection. It is hardly necessary to state that the patient should be stripped to the waist. Special attention should be paid to the borders of the lungs. He should be made to breathe noiselessly through the mouth whenever loss of vesicular murmur occurs at both apices. This will exclude in some instances a "loss" of vesicular murmur due to exaggerated transmission of the breath sounds from the nasal region due to obstruction. A series of short, quick inspirations often aids in demonstrating a good vesicular murmur in superficial "breathers." Some excess of breathing is often present on the right side as low as the second rib and second vertebral spine, and the expiration may be a trifle prolonged. In these regions the vesicular murmur may even have a slightly bronchial quality, especially over the inner part of the first interspace. In persons who have never breathed properly the vesicular murmur may be weak on quiet respiration.

Changes may occur in the quality of the vesicular murmur, in the relative duration of its two parts or in the continuity and equality. The first change to be detected is often some harshness and increased loudness. This in most cases is constant increase of loudness or elevation of the expiratory murmur—prolonged high-pitched expiration. Grancher held that the earliest change is a constant weak, harsh, or wavy inspiratory murmur, due to an inflammatory swelling of the lining of the terminal bronchioles, which if sharply defined at one apex is very significant. Wavy breathing precedes weakened breathing, which probably occurs only when the area of infiltration has reached some size. A change in the vesicular murmur is often the only variation from normal found on auscultation. In many cases it is difficult to define this slight change.

Wavy, Jerky, or Cogged Breathing.—In some pulmonary diseases the vesicular murmur is not continuous, but "wavy." In pronounced cases the breathing is not heard for a time, and reappears and disappears several times in a single respiratory act. This has been termed cog-wheel or jerky breathing. The wavy quality occurs chiefly during inspiration, but at times may be heard in expiration. Wavy or cog-wheel breathing over the site of the lesion does not occur often in early stages, where the lesion is situated at the apex. Wavy breathing may be due to the forced inspirations, and heard only when such are taken. Under these circumstances it is usually muscular in origin and has no significance. When confined to one apex, however, it is very suggestive, and a patient with it should always be looked upon with suspicion. Wavy breathing over both sides is quite frequent in nervous patients and is no indication of disease. It is frequently heard at the base behind, especially on the left side.

Prolongation of Expiration.—The first change to be detected by auscultation in some cases is a prolongation of the expiration, often slightly raised in pitch, due to a constriction of the bronchioles.

Weakened Breathing.—Weakened or distant breathing at one apex is often a very suggestive sign. It may be due to extensive and numerous foci of disease, to pleuritic changes, or to the narrowing of a bronchus by pressure or by mucus which after coughing may be removed. In other instances, however, only after some days is the breathing of normal or increased strength. Feeble musculature causes weakened breathing throughout both lungs.

Puerile and Harsh Breathing.—This is also rather infrequent in early stages, and while found frequently on the unaffected side in advanced stages it is by no means an unfavorable sign, as in many instances it indicates compensatory action.

The "metamorphosing" breathing is that form in which a change from a high-pitched to a normal vesicular quality, or *vice versa,* occurs during inspiration.

It is said to be pathognomonic of pulmonary tuberculosis, rare in occurrence, and due to a partial and momentary constriction of a bronchus by mucus.

When the disease becomes fairly well-marked the vesicular quality loses its pure tone and becomes more or less bronchial, the type of breathing most common in pulmonary tuberculosis, and spoken of as bronchovesicular or vesiculobronchial breathing.

Vocal Resonance.—The vocal resonance often varies directly with the vocal fremitus and, like the latter, is more pronounced on the right, to the level of the second or third rib and third vertebral spine, or even lower on the back. A slight increase on the right is therefore difficult to detect. The whispering voice as well as the ordinary tone should be very carefully auscultated over the entire chest, as small or deep-seated areas of consolidation are often first detected by this means. As the disease advances the vocal resonance passes through various gradations into bronchophony, and when excavation occurs whispering pectoriloquy is a very important physical sign.

Adventitious Sounds.—*Rales.*—It is rare to detect any adventitious sounds in the lungs in incipient pulmonary tuberculosis on quiet breathing. When rales are detected on quiet breathing the case is usually no longer in the incipient stage. *Rales are in most patients in incipient stages heard only during forced inspiration following cough, and may not be constant.* It is often necessary to explain carefully—best by example—to the patient how to cough in order to bring out clearly any adventitious sounds. He should be directed to cough with some force as noiselessly as possible and immediately after it to take a full, fairly rapid inspiration, contracting his muscles, and moving his shoulders during the whole procedure as little as possible. In certain cases a cough at the end of expiration followed by a full inspiration brings out rales heard in no other way. In some instances the rales are heard only on quiet breathing, in others they disappear after the first deep breath.

All varieties of rales are heard in pulmonary tuberculosis, but fine and moderately coarse are the most frequent. Resonant (consonating) rales occur over cavities, but may also be present where no other signs of cavity exist. Gurgling rales indicate either bronchial dilatation or cavity formation. While in early stages only a few fine rales, or a localized rhonchus, whining in character (Turban), heard with difficulty after coughing, above one clavicle, may be present; in advanced stages rales may be so numerous and so loud that the breath sounds are completely obscured. The "mucous click" is common in advanced pulmonary tuberculosis and is said to indicate softening. Moderately coarse rales may be transmitted from one side to the other.

Rales are most frequently heard first above or below the clavicle, slightly more often on the right side. The supraspinous area is often early involved and should be carefully examined. Very often a few rales, fine or moderately coarse, are heard after coughing in the infra-axillary region on the affected side. They may persist for some time, and after the diagnosis is made too much importance should not be attached to them. In some instances rales are heard only when the patient is in a reclining position (Stanton, Ransom).

Pleuritic friction, except that variety simulating intrapulmonary rales, is rare in early stages, possibly because of the apical location. Moderately coarse, superficial rales may be heard over the entire chest with absence of all sputum. This can be explained in two ways: first, that the sounds are of pleuritic origin; second, that the exudate is absorbed. Creaking and rubbing sounds, believed by many to be produced in the lungs themselves, are difficult to separate from pleuritic friction sounds and deep-seated rhonchi.

Cardiorespiratory murmurs are frequently mistaken for pathological wavy or interrupted breathing. If they occur at the left base with no other signs of disease, any connection with pulmonary disease can be excluded. Wide transmission of the heart sounds indicates a very forcible beat or beginning infiltration of the pulmonary tissue.

Post-tussive suction, a peculiar high-pitched, sucking sound occurring during the first part of inspiration following cough, is heard not uncommonly over cavities. It does occur in the chest, however, in which no

other signs of cavity exist. The *veiled puff* is a "single, rather high-pitched sound, of a puffing character, which becomes suddenly audible toward the end of inspiration" (Fowler). It is said to be a valuable sign of a small sacculated bronchiectasis.

Röntgen Rays.—The chief value of the *x*-ray examination is for diagnosis, but it may yield valuable information during the course. It reveals deep-seated cavities, congestion, enlarged bronchial glands, or beginning disease in the opposite lung not discovered by ordinary physical examinations. It thus aids in prognosis but should be relegated to the *x*-ray expert.

Latent Pulmonary Tuberculosis.—Physical signs may be entirely lacking. "Closed" pulmonary tuberculosis belongs here—"closed" because tubercle bacilli are not found (ulceration or "opening" of the focus has not occurred). In a majority, however, slight suggestive physical signs are present, though taken alone they may not be sufficient for diagnosis. A percussion note a trifle high-pitched and short above the clavicle, localized increased resistance, a shrinking of the resonant area above the clavicle, lessened diaphragmatic movement on one side, a slight deficiency in the vesicular murmur, and possibly a few fine rales clearing up on coughing are the most common signs. Any one of these may occur alone. In other words, the physical signs in this stage are often simply suggestive and suspicious and indicate further investigation. The so-called "pretuberculous" stage often belongs to this group.

Early (Incipient) Pulmonary Tuberculosis.—The physical signs have now become more pronounced; there is lessened movement at one apex, with slight dulness, a few fine or moderately coarse rales, heard in most instances only during the inspiration following cough. The change in the vesicular murmur is more marked and, besides high-pitched prolonged expiration, the inspiration may be changed and bronchovesicular breathing may occur. Wavy or weakened breathing may be present. The vocal fremitus and vocal resonance are both likely to be increased. In other words, persistent signs of local bronchitis at one apex are usually the first positive physical signs, although others are quickly added.

Advanced Pulmonary Tuberculosis.—All physical signs to be detected in the lungs may be heard at one time or another in advanced cases. One apex may present very early signs, while the other is in an advanced stage of the disease. In any case, however, the "physical signs" usually refer only to the most advanced lesion in the lungs. In rare cases either dulness or rales may be entirely absent. Hyperresonance may occur.

Softening.—The physical signs of "softening" are very uncertain. An increase in the size of the rales and a metallic quality or ringing character are said to indicate softening as well as the moist or dry crackling. The condition of the surrounding tissue modifies many of these physical signs.

Signs of Cavity.—These depend largely upon its size and location, and the condition of the surrounding tissues. Cavities of fairly large size may be readily overlooked either because a stoppage of the bronchus prevents the entrance of air, or because the cavity is filled with secretion or deeply situated. Unless superficially placed or surrounded by

consolidated lung tissue, it is not possible to diagnose cavities smaller than a walnut. Except in acute pulmonary tuberculosis, cavities may be assumed to be present practically always in the last stages, but often are discovered only at necropsy.

Inspection in no way differentiates cavity formation from fibrosis. In some rare instances more local bulging and retraction than is usual occur in a limited area on coughing. The note over a cavity may be normal, dull, flat, tympanitic, or amphoric. Change in tone may occur with change of position (change in position of liquid contents, etc., Gerhardt), with opening (higher note) or closing (lower note) the mouth, *i. e.*, mouth breathing (Wintrich), or with respiration (higher during inspiration), and may disappear if the tension of the wall is very great (Friedrich). Turban believes that Wintrich's and Gerhardt's changes of pitch are the most reliable signs of cavity. Change of position, leading to occlusion of the bronchus by the fluid contents, may obliterate many of the signs of cavity or lead to its diagnosis by emptying the cavity. The cracked-pot note is frequent over superficial cavities with a narrow opening into a patent bronchus situated in the upper lobe anteriorly between the clavicle and fourth rib, and is rare in cavities elsewhere. On auscultation the respiratory murmur may be intense, distant, or even absent, but is usually tubular, amphoric, or cavernous in quality. While auscultating a cavity the cavernous breathing may be quickly replaced by tubular breathing, only to yield in turn again to cavernous breathing. The metamorphosing breathing of Sietz may occur.

Coarse, bubbling rales are most characteristic of large cavities partially filled with secretion. Sharp, ringing, metallic rales are more frequent in smaller cavities, and may be heard only after cough. In old cavities, hisses, creaks, sonorous and sibilant rhonchi may replace all other rales, and in a few cases there may be no rales at all. The metallic tinkling sound occurs but rarely. The veiled or especially the cavernous puff may occur. Post-tussive suction is frequent. Clicks or gurgling sounds may be heard over cavities in the left upper lobe synchronous with the heart impulse. The voice sounds over a cavity are usually much increased, bronchophony practically always occurring. Whispered pectoriloquy, of low pitch and blowing quality, is one of the most trustworthy signs of cavity. The vocal resonance is quite commonly amphoric or cavernous. In cases with a chronic cavity the area of cardiac impulse may be greatly increased, and in some instances with cavity on the right side the point of maximum impulse may be as far out as the right nipple line. Hippocratic succussion and the coin sound may be heard over large cavities, and in some instances pneumothorax has been diagnosed. The physical signs of an apical cavity may completely disappear in front and be heard only at the apex posteriorly, or more rarely disappear entirely. A cavity may be overlooked if the patient is not made to cough and so remove a plug of mucus in the bronchus leading to the cavity. On *x*-ray examination, cavities if empty and if not surrounded by too thick a layer of diseased lung appear as light areas.

Signs of "Activity," "Arrest," and "Cure."—It is impossible to tell from a single examination whether the disease is progressing or retrogressing.

The physical signs may suggest great activity when the disease has been inactive for months. The contrary is also true.

Lungs once affected with tuberculosis are seldon if ever "cured" in an anatomical sense. Some patients with incipient disease after a lapse of months present no physical signs, but a few of those in advanced stages recover without pulmonary scars detectable by physical examination (*e. g.*, signs of consolidation, emphysema, etc.). It is remarkable what extensive physical signs may be found in patients who have enjoyed years of good health who may go on to permanent arrest and remain well for years with no diminution of the physical signs. Most patients present slight retraction of an apex or base, some dulness on percussion and loss of vesicular murmur which may even pass into bronchial breathing. Pleuritic sounds may linger in various regions, but it is still questionable how soon a patient with rales over any extent of the chest can be said to be "cured."

Myoidema.—This occurs in two forms, nodular and fibrillar or fascicular. In the incipient stages myoidema is usually absent. It may occur only on one side or more on one side (usually the side affected) than on the other, and may disappear as a fatal termination approaches. It has little importance, but when present demands a careful general examination of the patient, especially of the lungs.

Hippocratic Fingers.—Clubbing of the fingers with down-curved nails is usually a late manifestation and occurs in cases of long standing. The toes are often affected, and the nose may be involved. The base of the nail is palpable when the distal extremity is pressed upon.

Hypertrophic Pulmonary Osteo-arthropathy.—This is rare in pulmonary tuberculosis. The small joints of the hands and feet are usually affected, but the wrists, elbows, and rarely the hips and shoulders may be involved.

THE MODES OF ONSET

The exact time of onset, except in acute cases, can rarely be definitely determined. In a large majority, signs of failing health long precede symptoms localized in the lungs. Only a careful inquiry brings out these facts, which seem in many instances to have entirely escaped the notice of the patient. For this reason the onset in regard both to time and to symptoms is diffieult to determine exactly, and King has pointed out the great discrepancy between the onset described by the patient and the probable onset. Many have at the onset or early in the disease some symptoms or group of symptoms which characterizes the disease at first and enables us to divide them into several groups, which are not sharply differentiated and often combined.

Insidious or Latent. — Careful inquiry will often reveal symptoms of slight ill-health preceding for weeks, even months, the so-called "primary" hemoptysis, pleurisy, or acute febrile attack. The patient begins gradually to run down in health; he tires more easily, has less strength, loses a little weight continuously, and constantly has slight elevation of temperature in the afternoon; his appetite is poor, and if he lives in certain localities, is told he has a "touch of malaria." Undoubtedly

many recover at this stage, which fact throws more obscurity about the recognition of this type of onset. This latent group would undoubtedly include a large majority of all cases if a careful history were taken. In some instances serious disease in other organs masks the onset of pulmonary tuberculosis. The importance of the recognition of this group cannot be overestimated, for in early recognition lies cure. The succeeding two forms of onset are closely related to the latent type.

Glandular.—Recent research has shown that the bronchial glands may be affected shortly after the cervical, and that tuberculous disease of the bronchial glands is closely associated with—some hold an almost constant precursor of—pulmonary tuberculosis. As a rule, only cases with marked glandular involvement or suppuration should be included in this group. The existence of a few slightly enlarged cervical nodes does not constitute a "glandular" onset.

Onset following Fistula in Ano.—In a number of cases a suspicion of pulmonary tuberculosis is first aroused by the development of an ischiorectal abscess with a resulting fistula. The lungs on examination are found tuberculous, but in many instances the symptoms were so slight that they drew no attention to the lungs.

Catarrhal.—This is unquestionably the most frequent. A large majority of patients give a history of repeated colds, an attack of slight persistent bronchitis, or of "grip," as the earliest symptom. Many of these attacks may light up a slumbering tuberculous lesion. In some instances this onset closely resembles an attack of asthma. A history of cough during the winter for several years is not uncommon, and its persistence during the summer may first arouse the patient's anxiety.

Pleuritic.—Unquestionably, it is wise to treat all cases of idiopathic pleurisy with effusion as tuberculous, whether the effusion develops insidiously, slowly without pain, or acutely and with pain, whether with or without respiratory distress. The physical signs of intrapulmonary disease in these cases may be lacking, but slight signs at the apex should be conclusive. A long interval may occur between the attack of pleurisy and pulmonary tuberculosis, which suggests the possibility of a later infection. Dry pleurisy at one apex or double pleurisy is almost certainly tuberculous if no other exciting cause exists.

Hemoptoic.—In some cases the first symptom undoubtedly is hemoptysis, which may occur only once or repeatedly several years before other pulmonary symptoms or signs develop or may be followed by constitutional and local symptoms.

Laryngeal.—Tuberculous laryngitis is rarely a primary lesion, but in an important group of cases the laryngeal symptoms, hoarseness, aphonia, pain, and dysphagia, may entirely mask the pulmonary symptoms.

"Malarial."—Chills, fever, and sweats at the onset occur in a number of cases. The attacks are usually quotidian and may closely resemble those of true malaria. In some instances the chills and fever occur irregularly and rarely every two or three days.

Nervous.—In patients markedly neurotic the nervous system may be early affected by the tuberculous toxin. Neurasthenia is common and may obscure the other symptoms.

Febrile.—Slight but persistent fever is at times the only symptom at onset. In other cases the fever may be pronounced for some days and the patient profoundly prostrated, suggesting in some instances typhoid fever (typhoidal onset).

Anemic or Chlorotic.—Severe anemia or chlorosis with its associated symptoms may be marked at the onset, especially in women, and lead to a diagnosis of a primary anemia. Chlorosis has become much less frequent with more exact methods of diagnosis of pulmonary tuberculosis.

Gastric.—Loss of appetite, nausea, some vomiting, great discomfort after eating, distension or an acid dyspepsia with eructations, may be the only symptoms for a longer or shorter period. Emaciation is more rapid than is usual in simple dyspepsia, and the symptoms frequently disappear when the pulmonary tuberculosis is treated.

Diarrhœic.—The onset with diarrhœa, while not common, is often well-marked. It rarely precedes expectoration and slight cough, but predominates all other symptoms. In some cases the swallowed sputum causes an early intestinal tuberculosis which may be the chief symptom throughout, but more often a catarrhal enteritis is set up. This form of diarrhœa may continue for months and the patient lose but little weight.

THE COURSE AND DURATION

Course.—The primary seat of pulmonary tuberculosis is practically always near the apex of the lung, and as the disease progresses the lesion extends downward. In the more chronic and fibroid cases a definite course is often pursued, but in the acute and caseous forms the disease may spread directly from lobe to lobe. The three most frequent sites of the primary lesion are (1) just above or below the clavicle, $1\frac{1}{2}$ inches below the summit, rather nearer to its external and posterior borders, (2) the supraspinous fossa, and (3) the first and second interspaces below the outer third of the clavicle (rare).

When the disease begins above or below the clavicle, its usual course of extension is first to the apex posteriorly, then downward along the sternum and along the spine as far as the apex of the lower lobe (to the level of the third or fourth vertebral spine). The entire upper lobe is then involved, but even before this occurs the apex of the lower lobe (opposite the fourth and fifth vertebral spines) may be affected. The physical signs may then quickly extend to the base, where for some time a few rather superficial rales, chiefly in the infra-axillary region, may have existed. The signs in the apex of the lower lobe may clear and the patient coming under observation is thought to have a basal affection, due possibly to a different cause than that of the apical lesion. It is not infrequent to have a few signs develop at the opposite apex just as the signs at the apex primarily affected disappear.

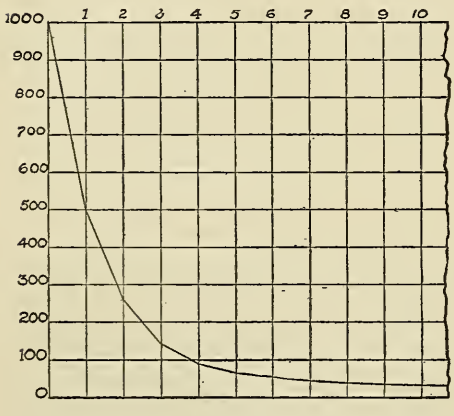
If the disease begins posteriorly the apex of the lower lobe is usually more quickly affected. Otherwise, the course is similar to the foregoing. The lesions in most cases are, according to Fowler, much more advanced posteriorly than anteriorly. This is not by any means always the case. When the apex of the lower lobe is affected the signs may not extend

downward parallel to the spine, but along the border of the outward rotated scapula (the position it assumes when the hand is placed on the opposite shoulder and the elbow elevated).

When the opposite side has become involved an area of tubular breathing with whispering bronchophony and resonant rales is frequent in the third and fourth interspaces just outside the nipple line. The physical signs often simulate those of cavity, but later in many cases the only physical signs remaining are a few fine rales. While frequent on the left side, this condition is rarely met with on the right, and may in some cases be the first point affected on the opposite side.

In a few cases the apex of the lower lobe is the first part of the opposite side to be affected. This may be due to a secondary infection, in which cases the lesions assume bizarre locations. Basal lesions usually mean a secondary infection from an undetected primary focus or an overwhelming primary infection. The disease usually quickly advances in the latter case to excavation, and infection of the opposite side occurs early. The incipient stage of pulmonary tuberculosis may last but a few weeks, but on the average may be said to extend over several months (up to six) and in a few instances may last for years. Some patients who have made perfect recoveries from an advanced stage of the disease may be later found to present signs of incipient disease on relapse.

FIG. 10



Proportions of dead and living, of all persons dying from pulmonary tuberculosis: 1, 2, 3, etc., years after onset of the disease, based on State, municipal, and private records of death. The curve follows approximately a straight line after ten years and falls to the base line at forty-one years, the longest duration among the records used being forty years.

Duration.—Pulmonary tuberculosis may last but a few days or extend over sixty or more years; the majority of cases, however, run a chronic or subacute course, with more or less frequent acute attacks. The average duration of the acute cases is between three to six months, but many die in less than four weeks. For all cases, acute, subacute, and chronic, the duration may be said to approximate three or four years, while for the chronic it is over twice as long.

Modern treatment has unquestionably greatly prolonged the duration, and this fact may be held to account in part for the decreased tuberculosis mortality of recent years. Acute tuberculous pneumonia and bronchopneumonia usually last from eight to twelve weeks. From a study of recent statistics (compiled by E. G. Pope), Fig. 10 has been constructed. This shows that about 35 per cent. of all patients die in six months, 50 per cent. in one year, 91 per cent. in four years, and 3 or 4 per cent. live from ten to forty years. Sex seems to exert no influence.

Pulmonary Tuberculosis at the Extremes of Life.—Long recognized as common in children, the frequency of pulmonary tuberculosis has often been overlooked in the aged. The difference in the course of the disease from that in the adult is marked.

In Children.—Pulmonary tuberculosis in children is of frequent occurrence and much more common during the first year of life. Louis' law, that when a caseous focus occurs in the body the lungs are found to be practically always tuberculous, does not hold in children, as Barthez and Rilliet's figures show that in 28 per cent. of cases of tuberculosis in children the lungs escape. Henoch would substitute "bronchial glands" for "lungs" in this law, which he would then uphold. If the symptoms continue until death the lungs are always affected.

In a large proportion the disease first attacks the bronchial glands whose early involvement and the patency of the lymphatics aid in generalization and prevent localized inflammation and resulting fibrosis. The younger the child the more diffuse is the disease, as a rule, while in older children it is more nearly similar to that in adults. The localization primarily at the apices is not present in children, but is often most marked in the upper or lower lobe, about the hilus of the lung.

Acute processes predominate in these cases in early childhood and several distinct forms can be recognized. A latent form in which the only symptoms are emaciation and fever is not rare and pulmonary signs may occur, but only shortly before death. The pneumonic (lobar) form is rather rare, but the bronchopneumonic form is of frequent occurrence. The pneumonic and miliary forms may differ little from similar types in the adult. The bronchopneumonic form may closely simulate simple bronchopneumonia, and if the sputum, obtained from the pharynx by a swab if necessary, the stomach contents, or the feces, contains no tubercle bacilli the diagnosis may present many difficulties. Expectoration is rare under seven and hemoptysis under five. Pleurisy and night-sweats are not frequent. The spleen may be enlarged and intestinal infection is common. Genital tuberculosis is rarer than in the adult, but meningeal complications more frequent. Death may occur in one to three weeks in the acute, but the more protracted cases may last from one to three or even six months. In some instances the child may become suddenly ill while teething or during convalescence from fever. There is then a rapid rise of temperature and signs of consolidation; death may follow in a few days (Osler).

Chronic tuberculosis, rare in children under five and not at all frequent until ten or twelve, runs also in unfavorable cases a shorter course than in adults. In many children a remarkable tendency to recovery is often manifested and under sanatorium treatment children as a rule do better than adults. The physical signs are often misleading and cavity formation is rarely recognized under three years, but after the age of eight its signs differ little from those of the adult. Death takes place usually from the occurrence of one of the acute forms of the disease, from meningitis, or from simple acute bronchopneumonia.

In the Aged.—Senile pulmonary tuberculosis is characterized by a slight tendency to generalization, a marked production of fibrous tissue, and

a lessened tendency to degeneration. The disease runs often a very chronic course and may be discovered only by accident in the course of what was thought to be chronic bronchitis, emphysema, or asthma. The examination of the sputum may alone establish the diagnosis. An acute course, however, is not rare. Fever is usually slight or absent in the more chronic forms, cough frequent, and expectoration abundant.

Termination.—This may be in cure, arrest, or death. The use of the word "*cure*" in this connection has met with much opposition, and in the sense of a *restitutio ad integrum* is certainly misleading. The inexorable test of time proves that many "cures" are only "arrests," and at least two years should elapse before the patient is said to be more than *apparently* cured, or the disease arrested.

Patients who recover without any persisting physical signs are chiefly those whose lesion is very slight, or is so deeply seated that it presents at no time physical signs, the diagnosis being made from the sputum. The majority of patients usually have collapse above or below a clavicle or flattening elsewhere, slight dulness, some change in the vesicular murmur (weakened, rough, or even slight bronchial breathing), possibly increased vocal fremitus or resonance, and in many cases a few fine rales. These signs may persist for ten to fifteen years after the patient has resumed his usual occupation in his home climate. Cough and expectoration may not entirely cease, and in many cases in which they do the patients are subject to bronchitis. Capacity for work is no criterion of cure, but subjective well-being is important. As long as caseous material is present in the lesion, viable tubercle bacilli may occur and a cure is not accomplished. Cavities of any considerable size rarely, if ever, completely close, but it is not unusual for the physical signs of excavation to become less-marked and finally entirely disappear.

Arrest.—Pulmonary tuberculosis in the vast majority of cases can never be said to be even "*apparently*" cured. Few chronic cases, however, progress so steadily that they cannot be said to be "arrested" at some time in their career. These arrests, however, are frequently only temporary. Arrest can occur when all hope is seemingly past, and every physician can recall the permanent arrest of the disease in one or more patients whom he has pronounced hopelessly ill. In fact, in some instances a self-limitation of the disease is strongly suggested.

Death.—The majority of patients (90 per cent.) with confirmed pulmonary tuberculosis die sooner or later from the disease or from one of its complications. Death by asthenia is the most common form. Death from asphyxia forms 4 per cent. of all deaths; it is more common in acute miliary and pneumonic phthisis than in chronic pulmonary tuberculosis. It may follow an acute exacerbation in a patient doing well. Sudden death occurs in a small percentage of cases, in which at postmortem no gross lesion sufficient to account for it can be found.

Death from complications occurs in many cases. Of these hemoptysis is not infrequent (14 per cent.). Death may be almost instantaneous from loss of blood or from asphyxia, or follow in a short time after repeated hemoptyses from exhaustion. This form of death seldom occurs in the early stages and rarely follows immediately upon sudden exertion.

Syncope occurs in about 5 per cent. and frequently after pneumothorax, which is the cause of death in 1 per cent. of cases. Empyema is rarely the cause of death, and when present usually follows pneumothorax. Meningitis (the cause of death in 3 per cent.) may develop and run its usual course. Other rare causes of death are intestinal perforation and peritonitis, and thrombosis or embolism of the pulmonary arteries.

THE CLINICAL FORMS

It is difficult to separate the acute forms from the chronic processes, and subacute forms are recognized. An acute onset is not infrequent in chronic cases. The classifications are numerous. Some are based upon clinical data alone, others upon pathological findings, but the most satisfactory take both into consideration.

The following classification has been used in this article:

I. Acute miliary tuberculosis.
II. Acute pulmonary tuberculosis.
    1. Pneumonia.
    2. Bronchopneumonia.
III. Subacute pulmonary tuberculosis.
IV. Chronic pulmonary tuberculosis.
    1. Chronic ulcerative pulmonary tuberculosis.
    2. Fibroid phthisis.

I. **Acute Miliary Tuberculosis.**—To many there is an appearance of mystery in the manifestations of miliary tuberculosis; it is set apart as something quite different from the more common chronic forms. If, however, comparative conditions in other infections are kept in mind this difficulty is not so great. If the relation of local infections with a pyogenic organism to pyemia be considered, we have some basis for the explanation of this form of tuberculosis. Hence, it may be considered as an acute, general infection, usually showing signs analogous to those of septicemia. The special features in any particular case may be very various and depend both on the acuteness of the infection and the distribution of the bacilli. Thus, if the bacilli enter the venous circulation they will reach the lungs especially, if into a pulmonary vein they will be distributed through the general circulation, and if into the portal circulation they may be deposited in the liver. In the great majority of cases the general infection is secondary to a primary focus somewhere in the body. Primary, general miliary tuberculosis may occur, but must be very rare; infection through the tonsil, for example, may be possible.

Given a local focus of tuberculosis there is always the possibility of this infecting the blood stream and so setting up a dissemination of the tubercle bacilli throughout the body. When we consider how many local lesions there are, the wonder is not that miliary tuberculosis occurs, but that it occurs so rarely. But this general dissemination gives a totally different picture from that of the sum total of a number of local lesions. A patient may have tuberculous disease of many organs, but

the results are quite different if these same organs are concerned in miliary tuberculosis. Some would consider it as an infectious disease with the bacilli carried throughout the whole body rather than as only a general distribution of tubercle bacilli. It is evident that the clinical picture may vary greatly, depending on the severity of the infection and the special distribution of the bacilli.

Etiology.—In the majority a previous focus must be regarded as essential, although infection through the tonsils or by way of the cribriform plate of the ethmoid may be possible; these must be regarded as unlikely. The most frequent lesion is in the lungs (given as 50 per cent. by some observers; it is said to occur in 3 per cent. of all cases of pulmonary tuberculosis). Glandular tuberculosis probably comes next in frequency, and then joint, bone, genito-urinary, and pleural lesions.

Of exciting causes the acute infectious probably take first place, especially measles and whooping cough. Typhoid fever is held by some to have an important influence, but the chances of incorrect diagnosis should be kept in mind. Trauma, operations, especially upon the bones, pregnancy, and debilitating conditions are all at times of importance. Occasionally, it has followed the rapid absorption of a pleural exudate. In patients suffering from chronic maladies, such as arteriosclerosis and nephritis, a terminal acute miliary tuberculosis is not uncommon.

Age and Sex.—Age has an important influence. The largest number of cases occur in early life, especially of the meningeal form. Sex appears to have no influence.

Incidence.—This is difficult to give. Among 1440 cases of tuberculosis of all kinds in the medical service of the Johns Hopkins Hospital in eighteen years there were 60 diagnosed as acute miliary tuberculosis, of which 29 were of the meningeal form. Among the 1440 cases, 980 were of pulmonary tuberculosis. There were 43 cases of generalized miliary tuberculosis among 417 autopsies at the Royal Victoria Hospital, Montreal (J. McCrae), on individuals who had some form of tuberculosis.

It is convenient to consider the disease under two forms: first, that in which the general features predominate, the general or typhoid form; and, secondly, those in which local symptoms dominate. Under the second the most common are the pulmonary and meningeal forms, although others have been described, depending on the predominance of signs in one system, as, for example, the pleura or peritoneum. It must be remembered that these divisions do not always hold and that some show features of two of them.

General or Typhoid Form.—The picture is that of an acute general infection without any marked local signs. The onset is usually gradual, with great malaise, headache, anorexia, and perhaps cough, chills, and digestive disturbances. With this there is fever and often an increase in the bronchitis. The temperature is usually irregular, and there may be intermissions of two or three degrees. The irregularity may be varied, the temperature being elevated fairly constantly for some days, and then showing marked remissions. Persistent high fever is usually seen in very acute cases without much involvement of the nervous system. In some the temperature may fall to normal or even below it at one period

of the twenty-four hours. An inverse type of fever is occasionally seen and rarely the course is afebrile. As the disease progresses emaciation becomes marked, there may be delirium, the tongue is dry, the pulse rapid but rarely dicrotic, and the picture is one of severe toxemia. The nervous symptoms are usually marked; restlessness, delirium, subsultus, and hyperesthesia may be present, with more tendency to dulness and coma. Choroidal tubercles may be present. The respirations are usually increased in frequency and the bronchitis becomes more severe. Dyspnœa and slight cyanosis are common and may be present without any marked involvement of the lungs. Cheyne-Stokes breathing may be present late in the course. The pulse rate is usually high and the heart sounds become feebler, with the first much like the second. Anorexia is usually present and occasionally vomiting. There may be diarrhœa and intestinal hemorrhages. Meteorism is not uncommon and the spleen is usually enlarged. Tubercle bacilli can often be obtained from the blood drawn from the spleen, although this is not a procedure to be advised. The urine contains albumin and the diazo reaction is often present. The blood usually shows a leukocytosis and tubercle bacilli may be obtained in cultures. Occasionally there is a hyperemic rash, sometimes in the form of small spots, which may simulate the rose spots of typhoid fever, but it does not come out in crops. Late in the course petechiæ may appear, especially about the wrists.

As the disease progresses the symptoms of pulmonary or meningeal involvement may appear. The course is usually progressive without any period of improvement. The average duration is about four weeks, with usual limits of one to six weeks.

Diagnosis.—This may present difficulty in the distinction from any severe infection, but the diagnosis from typhoid fever must be considered as the most important. Miliary tuberculosis is more likely to be regarded as typhoid fever than the reverse. The obtaining of typhoid bacilli from the blood, urine, feces, etc., and the Widal reaction are most important. The temperature curve is usually more constant in typhoid fever; remissions are more marked in miliary tuberculosis. Dyspnœa and cyanosis are usually more evident in miliary tuberculosis. The presence of typical rose spots is of course important. The spleen may be enlarged in both, although more frequently in typhoid fever. Leukocytosis is more common in miliary tuberculosis, and the large relative increase in the mononuclears present in typhoid fever is not found. The result of lumbar puncture may be of help, as either typhoid or tubercle bacilli may be found. The finding of choroid tubercles may give the diagnosis.

Treatment.—This can only be symptomatic, and it seems hopeless to endeavor to influence the disease by any therapy.

Pulmonary Form.—In this the pulmonary symptoms predominate and may be severe from the onset. The picture may vary, depending on the relative severity of the general toxemic symptoms and the condition in the lungs. The onset may be sudden, occasionally with chills, and the temperature rises to 102° to 104°. It is usually irregular and an inverse type may be seen. In patients with previous marked tuberculous lesions

the fever may increase gradually. The disease usually begins with the symptoms of acute bronchitis, or in children those of bronchopneumonia. There is shortness of breath and a dyspnœa quite out of proportion to the physical signs. It has been suggested that this may be due to irritation of the vagus by tubercles. There are occasionally asthma-like attacks and sometimes Cheyne-Stokes breathing. The cyanosis is usually very marked and may be intense. There is considerable cough with expectoration, which is usually seropurulent or mucopurulent, and sometimes even rusty. In a few instances hemoptysis has occurred.

On examination, inspection may show good expansion with full interspaces. Percussion usually gives a full note, which may be quite hyperresonant, especially over the anterior margins of the lungs. In some cases the hyperresonant note is obtained over certain areas; this is especially the case in children if there is some bronchopneumonia. On auscultation the breath sounds are harsh, but may be almost obscured by the adventitious sounds. These are usually heard everywhere, and at first, fine, often very intense, crackling rales predominate. Fine crepitations have been thought to be due to tubercles on the pleura in some cases. There may also be sonorous and sibilant rales, while with the progress of the condition the rales may be coarser and moister. If there are areas of bronchopneumonia, tubular breathing may be heard over them. The sputum may contain tubercle bacilli, possibly from the primary focus, if this be pulmonary. Only in prolonged cases can they come from breaking down of the miliary tubercles.

The pulse is rapid and feeble. The heart sounds are clear, but may be obscured by the rales. Choroid tubercles have been found. The spleen is usually enlarged. The course of this form may be rapid, but in some the progress may become more chronic and last even for months.

The *diagnosis* may offer no difficulty. In some the absence of any definite physical signs, the association of rapid breathing, dyspnœa, and cyanosis, excites suspicion. In some cases of bronchopneumonia, especially in children following one of the acute infections, it may be difficult. In some instances lobar pneumonia may simulate this disease, but careful examination should prevent error. In bronchitis occurring in elderly people, especially with marked emphysema, there may be difficulty for some days. The intense bronchitis of typhoid fever, especially if associated with early severe toxemia, may cause confusion, but other signs are likely to make the diagnosis clear.

Meningeal Form.—Tuberculous Meningitis.—*Etiology.*—In the majority this is secondary to tuberculous disease elsewhere, although in a few it has been suggested that it is primary in the meninges. The acute infections are important factors in determining the onset.

Age.—This form usually occurs in young children below the age of four years, although it may be at any age. In a series of 52 cases studied by Koplik,[1] 11 were under one year. The average age was a little over four years. The age in 100 cases in children collected by Still showed in

[1] *Journal of the American Medical Association*, 1907, xlviii, 1149.

the first year 13, from the second to fifth year 70, and from the fifth to the tenth year 17.

Onset.—In the great majority this is gradual. If the disease follows one of the acute infections the conditions may merge into each other, or previous ill-health may have been due to an existing tuberculous lesion. In 86 per cent. of Koplik's series the onset was gradual. There is usually a history of the child not having been as well as usual, or perhaps there was loss of weight, irritability, anorexia, lassitude and restlessness in children, and in adults a change in disposition, headache, and malaise. The symptoms of a gradual onset may be present for some weeks. Occasionally, older children and adults may show slow cerebration, perhaps with some affection of speech. In some instances the history may be of sudden onset, with fever, chills, vomiting, and perhaps convulsions, but this is rather exceptional. An injury may apparently be the determining factor.

The course has been usually described in three stages: (*a*) *The stage of irritation.* In this there is fever, which is often remittent, headache, vomiting, and perhaps convulsions. The child may be restless and much disturbed by twitching of the muscles. The headache may be very severe, and in a child the hand is often put to the head with the utterance of an unusual cry. This is a curious sound, often very characteristic, which has been called the hydrocephalic cry. Some patients scream constantly except when under chloroform. Vomiting may occur, but is not often very persistent. The bowels are usually constipated. There may be some rigidity or stiffness of the neck. The pupils are usually contracted. The pulse is generally rapid at first. (*b*) *The stage of cerebral pressure.* The temperature is variable. The irritative symptoms become less marked; the child is dull, difficult to arouse, and may be delirious. Retraction of the head becomes more marked. The pupils are dilated, and there may be ptosis or strabismus. There may be monoplegia or hemiplegia; in others there is rigidity of one side of the body. There may be convulsions. Vomiting may occur, and constipation is common. The abdomen is retracted, or, as it is often termed, carinated. The pulse is slow and at times irregular. The respirations are slow and sighing. Cheyne-Stokes breathing may appear. Various skin lesions are common, such as erythema and herpes. (*c*) *The stage of paralysis.* The coma increases and the patient is quite oblivious to the surroundings. Convulsions, either general or local, occur, and there may be paralysis of certain muscles. The pupils are dilated; optic neuritis and paralysis of the ocular muscles may occur. Diarrhœa is common, with incontinence of the urine and feces. The temperature is variable, and may rise to 105° or 106° or fall to subnormal, 94° or 95°.

It is not always possible to recognize these stages. The symptoms show so much variation that they are only more or less general and not necessarily sharply marked. The patient usually lies on one side, with the legs fixed on the body, and resents any attempt to alter this.

Nervous System.—The mental state, except in the early stage of irritation, is usually dull and apathetic. The patients pay little attention to what is going on around them. As the disease progresses the patients

may become unconscious, but often it is more a state of stupor. Occasionally a patient who has been comatose arouses for a time and may be quite conscious, only to relapse into coma. Hyperesthesia, so common in the epidemic form of meningitis, is usually absent. Pain in various parts of the body or limbs may be complained of by older patients. Headache is complained of by adults; in children its presence may be suspected by the crying and the movements of the hand to the head. Convulsions are often present at some stage or other. There may be irregular tetanic contractions of one extremity. Curious associated movements are seen. Some patients suck the lips or have repeated motions of the jaws. If paralysis occurs it is usually hemiplegic or monoplegic. There may be facial paralysis. In the eyes the third nerve is most frequently involved; in some cases this may be with paralysis of the face, limbs, and hypoglossal nerve of the opposite side.

Kernig's Sign.—This is by no means constant and was found in only 22 of Koplik's 52 cases. In this series the Babinski reflex in children over two years of age was more useful, being present in 23, and, if found, Koplik considers it an important aid in the recognition of the tuberculous form. The general reflexes are usually present until the later stage, when they disappear. Rigidity is present in the neck in the majority; it was absent in 14 of Koplik's 52 cases. It does not usually appear as early as in the epidemic form, and generally does not cause such marked retraction of the head. It may occur in the extremities. *Paresis* of the muscles usually comes on late in the course. There may be great variation in this condition from day to day.

Lumbar Puncture.—This usually gives results of the greatest importance. The fluid may be hazy, turbid, and under considerably increased pressure. Rous[1] in thirteen tests found a mean pressure equal to 308 mm. of distilled water (the normal is 120 to 180 mm.).

The protein content of the fluid is usually increased and may average 1 gram per liter. In some cases there is a substance present which reduces Fehling's solution. The most important point is the presence of tubercle bacilli. It may be said that the number of cases in which tubercle bacilli are found in the spinal fluid is directly proportional to the care with which they are sought. The fluid should be obtained free from blood, centrifugalized for a considerable time, the sediment stained and long search made in the prepared slides. In one series tubercle bacilli were found in 135 of 137 cases observed by Hemenway. The fluid may be injected into guinea-pigs, which is certain, but slow.

Cytology.—As a rule, the total number of cells is much increased. The most striking finding is the large percentage of mononuclear cells (usually over 90 per cent.). In rare cases the polymorphonuclear leukocytes may predominate, but no rule can be laid down as to any special significance of this. Aside from the presence of tubercle bacilli and a large percentage of mononuclear cells, the other information obtained by lumbar puncture may be regarded as rather more valuable in excluding tuberculous meningitis. When the pressure, amount of protein, and the cellular

[1] *American Journal of the Medical Sciences*, 1907, cxxxiii, 567.

elements are normal, these must be regarded as being strongly against tuberculous meningitis.

Percussion of the Skull.—Koplik has drawn attention to the importance of Macewen's sign in the recognition of internal hydrocephalus in young children. He found it present in 34 of 52 cases. In doing this the patient should be upright, with the head slightly inclined to one side, the skull being percussed over the pterion. The obtaining of a tympanitic note speaks for the existence of internal hydrocephalus. This sign may apparently be present comparatively early in the course.

Eyes.—Ptosis and strabismus may occur. The pupils are usually contracted in the early stages, but as the disease progresses become dilated, and toward the end may give no reaction to light. In some cases an oscillation of the pupils between contraction and dilatation is seen. The changes in the fundus are important. The disk may be swollen, with indistinct margins and the veins distended; or there may be optic neuritis, which is usually present in the latter part of the course. In two-thirds of Koplik's cases there was some change in the disk. The presence of choroid tubercles is the most important finding. The reports as to the frequency vary greatly, some observers having failed to find them in a number of cases. In 9 among 46 of Koplik's series they were found in the second day of active symptoms.

Duration.—This varies greatly. There are some cases, most often seen in adults, with a very rapid course, the acute features lasting only a few days. On the contrary, the duration may be prolonged, the condition becoming one which might almost be termed chronic meningitis. This is especially likely if the meningitis be limited, when psychical symptoms or those suggestive of brain tumor may predominate. The average duration may be stated as between three and four weeks. In some instances there are periods of improvement followed by relapse. In some of these cases the improved condition may be so marked that doubt is cast on the diagnosis, unfortunately only for a short time. In some the course is almost latent and the duration may be impossible to state.

Diagnosis.—This must first be made in regard to the presence of meningitis and secondly as to the variety. In the early recognition of tuberculous meningitis, the former of these is likely to give the greater difficulty. In children the symptoms at onset may be much like those of any febrile attack or gastro-intestinal disease. Headache, convulsions, vomiting without cause, respiratory signs, especially sighing respiration, a retracted abdomen, rigidity of the neck, Kernig's sign, and Brudzinski's sign, are all suggestive.

In children the exanthemata may give difficulty for a few days. The appearance of the rash of each disease gives the diagnosis. From typhoid fever, the more irregular fever, the absence of the rose spots, the Widal reaction, the decubitus—dorsal in typhoid fever, lateral in meningitis; the headache, complaint of which, as Sir William Jenner pointed out, ceases in typhoid fever with the onset of delirium, but persists in meningitis, and the results of lumbar puncture, all aid. Some cases of indefinite, continued fever in children, sometimes with glandular tuberculosis, may give difficulty for some time. The course and the

results of lumbar puncture are the greatest aids. In certain instances there has been great difficulty in making a diagnosis from hysteria, beginning mental disease, or delirium tremens. Some intracranial conditions may cause confusion, such as otitis media, thrombosis of the cerebral sinuses, cerebral syphilis, cerebral abscess, and cerebral tumor, especially if tuberculous. The absence of the most characteristic signs of meningitis and the results of lumbar puncture are important.

The diagnosis of meningitis being made, the recognition of its character as a rule offers less difficulty. By far the greatest aid is lumbar puncture. With care and perseverance, tubercle bacilli may be found in a large percentage of cases. In their absence the finding of a large proportion of mononuclear cells in the fluid is suggestive of the tuberculous form. The presence of a tuberculous focus elsewhere is of importance. The presence of tubercles in the choroid is positive. The examination for them should be made every day.

Prognosis.—The few recoveries which have been reported, even after the finding of the tubercle bacilli in the spinal fluid or of tubercles in the choroid, stand out as such exceptions, that the outlook must always be regarded as practically hopeless.

Treatment.—When the disease is established, the patient should be kept as quiet as possible, and in a darkened room if there be photophobia. It may not be easy to give food, and if there be difficulty in swallowing, the stomach tube may be necessary. In case of vomiting, various general sedatives may be given and rectal feeding employed. The ice-bag to the head may give relief to headache, but if this be severe, with great restlessness, or convulsions occur, bromide, chloral, or morphine, hypodermically should be given. A hot bath, at 105° to 115°, may be given every four to six hours. Blisters and other methods of counter-irritation are to be condemned. Lumbar puncture should be repeated at intervals, depending on the amount of fluid obtained, the degree of pressure, and the influence on the symptoms. Surgical methods, such as trephining or opening the spinal canal, have not met with sufficient success to justify their adoption.

II. **Acute Pulmonary Tuberculosis.**—The pulmonary form of acute tuberculosis can occur in two types, the pneumonic and the bronchopneumonic. Both constitute not more than 10 per cent. of all cases of pulmonary tuberculosis.

1. **Acute Tuberculous Pneumonia.**—This form, known also as acute phthisis, acute pneumonic phthisis, caseous pneumonia, and epithelial pneumonia, occurs more frequently in adults than in children, but is the rarest of the acute forms. Many cases are no doubt instances of confluent multiple foci, but in a few the disease invades a whole lobe at once. Males are more frequently attacked and are often robust and between twenty and forty years of age. The infection is usually bronchogenous, but may be hematogenous (Tendeloo). The onset, usually acute, and the course for some days closely resemble those of acute lobar pneumonia. A chill may usher in the attack and physical signs of consolidation of an entire lobe, usually the upper, develop in a few days. Herpes labialis is not uncommon (Kidd). The bronchial breathing has been described as

distant and suppressed, but in many cases this is not so. The sputum is frequently tenacious, rusty, and, in fact, for some days closely resembles that of lobar pneumonia. Pneumococci, but no tubercle bacilli, may be present, and unless a previous history of a pulmonary disease can be obtained a diagnosis of frank pneumonia is made. The crisis, however, does not occur, resolution is delayed, the fever assumes a more hectic character, the patient emaciates, and the sputum takes on a greenish tint. Tubercle bacilli have been found as early as the fourth day (Osler), but more frequently are not discovered until the crisis fails to appear. Elastic tissue is less frequently found than in caseous bronchopneumonia.

When the lower lobe is involved, signs of infiltration may be found at the apex; or if, as is more common, the upper lobe, an infiltration at the opposite apex. The actual physical signs, further, may not agree with the date of appearance of the disease. Dry tuberculous pleurisy is almost always present. The temperature is usually high, but remittent throughout, and from the first shows a wider range than is usual in acute lobar pneumonia which runs the same course in the tuberculous as in the healthy subject (Fox). The pulse is accelerated and ranges from 100 to 130, while the respirations vary between 30 and 40. Cyanosis is not usually present, but in cases of some duration, anemia of the lips and mucous membranes is common. The dyspnœa is much less marked than in the acute miliary type. Emaciation is often a prominent feature, and may be accompanied by great prostration. Hemoptysis sometimes occurs at the onset and may cause death. Albuminuria is infrequent, the diazo reaction rarely absent.

The duration may be but three or four weeks (Tendeloo had a patient die on the sixth day), but more usually it extends over three or four months. A few patients pass into the chronic stage and live for two to five years, but rarely if ever fully recover. The usual course is progressive. Death occurs chiefly from asthenia, which is frequently aggravated by tuberculous enteritis, laryngitis, and in a few cases from meningitis.

2. **Acute Tuberculous Bronchopneumonia.**—This form, described under the names of phthisis florida, galloping consumption, or caseous bronchopneumonia, is the more common acute type. In children and the aged it closely simulates simple bronchopneumonia, and the diagnosis may not be made for weeks.

The onset is occasionally acute, but more often insidious, with cough. When this acute form supervenes upon a more chronic type, as is common, it frequently follows hemoptysis and is due to aspiration. It not infrequently follows influenza, or, in children, measles or pertussis. The symptoms are usually pronounced. The cough in some cases, dry at first, soon becomes loose. The sputum, variable in amount, early contains tubercle bacilli and elastic fibers. The patient at first presents a rapid pulse, high, often fluctuating temperature, and quickened respiration. The physical signs, at first indefinite at an apex, soon become more pronounced, and when softening and excavation occur, which are rapid in many cases, chills and night-sweats are common. The patient rapidly emaciates and loses strength. Hemoptysis is infrequent, but diarrhœa is often present. Death may occur in three or four weeks, but the disease

may last three or four months, or the acute symptoms subside and the disease become chronic.

Three types of caseous bronchopneumonia can be recognized. The first occurs in patients already tuberculous, and is due to the aspiration of blood and secretions, often from an old, apical cavity. The resulting symptoms are those of a secondary infection. The second type (due also to aspiration and rarely to hematogenous infection) is the peribronchial or nodular. Small, solid, caseous foci, the size of a pea or walnut are found surrounding a bronchus. Diffusely scattered, fine rales, with little or no dulness, and sputum free from tubercle bacilli, are characteristic phenomena. The third form, the disseminated ulcerative type, frequently following diabetes, pregnancy, alcoholism, influenza, measles, or pertussis, usually terminates fatally in two to four months. It is frequent in children between two and six years of age. Death from hemoptysis, meningitis, or general miliary tuberculosis is usual.

III. **Subacute Pulmonary Tuberculosis.**—Comparatively few cases run an acute course from start to finish, but in a very large number the disease is never completely quiescent but smoulders along with an occasional acute outbreak. The symptoms lessen, the weight and strength increase, the morning temperature falls to normal or below, but each day at some time a temperature of 99.5° to 100° occurs. This may persist for weeks, but sooner or later it gives way to a return of the night-sweats, increased cough and expectoration, with possibly pleuritic pain or dyspnœa: the morning temperature no longer falls as low as normal, and the disease makes rapid headway for a few weeks. This may be repeated for one or two years, but with each successive attack the patient regains his lost strength and weight less readily, the dyspnœa is more continuous, and finally the whole of both lungs becomes involved. Finally and usually during one of the periods of acute exacerbation, the patient dies from asthenia or possibly some slight complication occurs which he is not able to resist. This type is frequent in developing females, follows the puerperium, or occurs when the constitution has been undermined by chronic disease, such as alcoholism, syphilis, or diabetes.

IV. **Chronic Pulmonary Tuberculosis.**—Chronic pulmonary tuberculosis, phthisis, consumption, includes the large majority of all cases of pulmonary tuberculosis. The course, extending usually over about ten years, is marked with many remissions and temporary arrests. Many chronic cases begin acutely and continue so for some little while. Every acute form may become chronic, even miliary tuberculoiss of the lungs. The distinction between acute and chronic forms depends largely upon the fever. In the first it is constant, remittent, intermittent, or even absent for a short but fleeting period. In the second it is absent for long periods and its recurrence is usually marked by an increase of symptoms. The disease may remain stationary at one place, or even improve, while advancing in another. Two well-defined subdivisions may be made: the ulcerative and the fibroid form.

1. **Chronic Ulcerative Pulmonary Tuberculosis.**—This form, the usual type, is characterized in well-marked cases by cavity formation and induration. The disease has usually long periods of quiescence, or arrest

may go on to cure. In other cases at infrequent intervals acute attacks occur, and in each a slight extension of the disease takes place.

2. **Fibroid Tuberculosis.**—Some cases of chronic pulmonary tuberculosis, lasting from ten to twenty years, or even longer, are characterized by the extensive formation of fibrous tissue which overshadows caseation or ulceration, if present, or entirely replaces the tuberculous changes. The most marked alterations in the shape of the chest occur in these cases; one apex or base may be greatly retracted, move little or not at all, and present marked dulness. The heart is often displaced, murmurs are common, and in some cases hypertrophy of the right side occurs, with possibly signs of deficient aëration, first noticed in the nails and lips.

Dyspnœa on exertion may be pronounced and dilatation of the bronchi is common. The cough is often paroxysmal and apparently, while effective, of little force. Fever may be absent for long periods or very slight when present. Hemoptysis is not infrequent. The onset is rarely acute.

Fibroid disease of the lungs was long looked upon as a pathological entity, but the fibroid changes are usually limited to one lung or a portion of one lung, rarely involve the whole or both, as is common in sclerosis of the liver or kidneys. Clarke in his monograph distinguished three forms of fibroid phthisis: (1) Tuberculo-fibroid, the generally accepted fibroid phthisis; (2) fibro-tuberculous, the fibroid disease supposed to be primary, the tuberculosis secondary; and (3) pure fibroid, without apparent cause of the fibrosis, a point criticised by West. Patients with fibroid pulmonary tuberculosis are threatened with three dangers: (1) Hemoptysis usually profuse; (2) extension or generalization of the tuberculosis; and (3) failure of the hypertrophied heart.

Latent Pulmonary Tuberculosis.—This term is used to include forms in which the symptoms or the physical signs may be latent. In the one the symptoms may be suggestive or even pronounced, but physical signs are often lacking on repeated examinations. On the other hand, a routine examination of the chest, often made on an applicant for life insurance, reveals the presence of well-marked physical signs, where little or no history of symptoms can be obtained (masked pulmonary tuberculosis). In either case, more often, however, in the former, the sputum may remain free from tubercle bacilli (closed pulmonary tuberculosis). In this group belong the cases of phthisis ab hemoptoë or sudden pneumothorax in apparently healthy patients.

A small number of patients present very indefinite pulmonary signs throughout the course. Tubercle bacilli occur in their sputum, and many show rather extensive changes on radiographic examination.

Chronic excavation may exist with every appearance of health. Cure rarely occurs after the formation of a cavity, but arrest is frequent, and many patients with a limited cavity at one apex enjoy years of comparative health. The physical signs gradually disappear from the front, to persist at the apex posteriorly for a long time. In other patients the cavity walls secrete profusely. Excavation of an entire lobe, unusual and more frequent in men, occurs equally on the two sides, but affects the upper more than the lower lobe. Complete excavation of an entire lung is very rare.

COMPLICATIONS

The complications of so chronic and debilitating a disease are numerous, as we would expect. They can be divided into those due to the action of the tubercle bacilli or its poisons and those due to other factors. Undoubtedly the complications caused by the tubercle bacillus are always of serious moment, indicating a weakened resistance. Secondary tubercle in primary lung disease may arise in one of three ways: it may be due to direct infection from contact with the sputum, *e. g.*, in the larynx, tonsils, nose, intestines; from direct extension of the disease, *e. g.*, into the pericardium, pleura, chest wall; or the bacillus may be carried, possibly in leukocytes, through the lymphatics or bloodvessels to distant organs. The infection transmitted by this last method may be localized in the brain, meninges, bones, ear, peritoneum, or lungs, or be generalized in the peritoneum, serous membranes, lungs, or throughout the body. The irritants in the sputum may produce bronchitis, tracheitis, laryngitis, pharyngitis, and if swallowed, gastritis, fermentation, and diarrhœa. When absorbed into the circulation they cause in some cases anemia, neuritis, atrophy, and fatty degeneration of the muscles and even of the heart. In late stages, thrombosis, dropsy, amyloid and other diseases, not peculiar to pulmonary tuberculosis, may occur.

Respiratory.—Secondary Infection.—The chronicity of the disease, the frequency of abnormalities in the upper respiratory tract, especially in the nose, the intercurrent bronchitis, the partial destruction of the ciliated epithelium of the lower air passages, as well as the frequency of microorganisms in the dust of buildings and cities, would all lead us to believe that, the usual defences being broken down, secondary infection is of frequent if not of constant occurrence. But not all cases of pulmonary tuberculosis even at necropsy show secondary organisms in the pulmonary lesion. Ravenel and Irwin have reported three cases of cavity formation which proved to be sterile. Ophüls reported seven out of thirteen. Many tuberculous lungs harbor harmless bacteria, which in no way influence the course of the primary disease. These should not be spoken of as instances of mixed infection, but the term should be reserved for those cases in which one or more secondary organisms exert some discoverable influence upon the symptom complex.

While secondary infections are usually looked upon as harmful, some hold that they may exert a favorable influence upon the pulmonary tuberculosis (Sata). It is probable that the prevailing secondary organism in patients in large cities is not always the same. Many and in fact the majority of the organisms which are almost constantly present in advanced stages have been shown to possess little or no pathogenicity for animals. The organisms recovered from the lungs are nearly always of low virulence, and in one instance a streptococcus obtained at autopsy, very virulent for animals, was found on subcutaneous injection into man to produce only local changes, suggesting those of an insect sting. Their effect, therefore, upon the patient is still not yet definitely determined, notwithstanding the claims of many competent authorities, who would

attribute to the secondary infection the disintegration of the pulmonary tissue (Prudden), and the fever, as well as an abundant expectoration and spreading pneumonia. It is impossible to exclude pre-agonal and post-mortem invasion by the secondary organisms in pathological specimens.

Microörganisms have formerly rarely been recovered with unimpeachable technique from the blood in pulmonary tuberculosis unless the patient was *in extremis*. A number of observers have recently obtained positive blood cultures by inoculating large quantities of blood into suitable media, but as yet no causative relation to the fever or symptoms of the pulmonary tuberculosis has been definitely established. Whatever results may later be forthcoming, the injection of tuberculin or of tubercle bacilli in pure culture may cause fever under such conditions that secondary organisms may be almost positively excluded.

Careful work has been done to determine the bacterial variation in sputum coincident with increase of symptoms but with negative results. Still the grave importance of some mixed infections cannot be questioned. On the whole it seems as if mixed infection was not as important as some would have, but that it is not to be neglected is borne out by the fact that the majority of patients with pulmonary tuberculosis do far better in the country, when removed from constant reinfection with secondary organisms from the dust of cities. Little light has been thrown upon this subject by the study of the patient's opsonic index to the various secondary organisms recovered from the sputum. If after vaccination with an organism to which the patient had a low opsonic index he showed marked signs of improvement, it might be justifiable to call such an infection "mixed" as well as "secondary." The favorable results following the use of vaccines have shown that in a few patients the infection was mixed.

Upper Air Passages.—The tendency to contract colds and other affections of the upper respiratory tract is very marked. Moeller and Rappoport have shown that in 120 patients with pulmonary tuberculosis the nose showed some pathological change in 84 per cent., the pharynx in 76 per cent., and the larynx in 42 per cent.

Tuberculosis of the Nasopharynx. — This uncommon complication usually attacks the cartilaginous septum, but may occur at the juncture of the skin and mucous membrane. *Pharyngeal tuberculosis* occurs as a complication usually late in pulmonary tuberculosis. The *tonsils* are frequently found at postmortem to be tuberculous, but as the condition gives no definite symptoms nor characteristic appearance it is rarely recognized clinically.

Larynx.—This is discussed elsewhere.

Aphonia.—This may occur from hysteria, a functional paresis of the adductor muscles of the vocal cords (especially common in women), from pressure of enlarged glands, bronchial or cervical, apical infiltration and shrinking, or pleurisy, upon the recurrent laryngeal and resulting paralysis (rare), and from mucus or secretion on the vocal cords (transitory), as well as from tuberculous involvement of the larynx.

Bronchi.—A large percentage of cases of fibrinous bronchitis occur in pulmonary tuberculosis, which has been considered an etiological

factor. Bronchitis may be said to be a constant accompaniment of pulmonary tuberculosis, and while in most instances it is due to irritation from the poisons of the sputum and secondary organisms it may be a true tuberculous bronchitis.

Pneumonia.—Simple *bronchopneumonia* occurs in many cases as a complication. *Acute lobar pneumonia* is, at least in health resorts, rarely diagnosed among the complications of pulmonary tuberculosis. It appears to be of more frequent occurrence in large cities. When it occurs in a tuberculous patient it may run its ordinary course and terminate either by lysis or more rarely by crisis.

Gangrene and Abscess.—These rarely occur in pulmonary tuberculosis (in less than 1 per cent., West). In a few instances the walls of a cavity become gangrenous, but this is much more unusual than the fetid decomposition of the secretions in cavities. Abscess also seldom occurs.

Bronchiectasis.—This, while rare in the more acute forms, is far from unusual in fibroid pulmonary tuberculosis.

Emphysema.—This is frequent in pulmonary tuberculosis and in some instances may mask it. Compensatory emphysema, however, is frequently found in chronic cases on the less affected side, and may be so marked that the lung extends well across the middle line.

Interlobar emphysema may occur. In rare instances caseation of a bronchial gland may lead to ulceration of a bronchus, or the rupture of an adherent cavity into the tissues of the chest wall may occur, which produces general subcutaneous emphysema. Death quickly results.

Atelectasis.—Areas of atelectasis are frequent in patients usually middle aged, in advanced stages, with shrunken chests.

Asthma.—Pulmonary tuberculosis may occur in an asthmatic, but asthmatic attacks are not infrequent when the tuberculous disease becomes chronic and the fibrosis pronounced.

Pleura.—Pleurisy occurring in tuberculosis has been grouped by Osler under three heads: (1) Acute tuberculous pleurisy, (2) subacute and chronic pleurisy, and (3) general serous membrane tuberculosis.

Dry pleurisy may be said to occur almost constantly from extension of the process to the pleura. It may be primary (miliary tubercle). The work of Hodenpyl leaves little doubt that the majority of obliterative pleurisies are tuberculous. Marked thickening of the pleura may occur, but this condition usually follows an effusion.

Pleurisy with effusion is far from infrequent in pulmonary tuberculosis, although it occurs much more frequently at its onset than during its course. The effusion is usually (80 per cent.) serofibrinous, but may be serous or in rare instances hemorrhagic, which betokens an unfavorable and usually rapidly fatal course (Moutard-Martin). Chyloform or milky exudates may occur. The effusion may be interlobar.

Pneumothorax.—Pulmonary tuberculosis is said to be the cause of 80 to 90 per cent. of all cases of pneumothorax. It is, however, a rare accident in the incipient stage, and postmortem figures, including a number of undiagnosed cases, show it to occur in about 5 per cent. of all autopsies in pulmonary tuberculosis. The lung must be at least partly free from adhesions, and usually a rapidly advancing caseous

process with cavity formation is found just under the pleura, at the point of rupture. Pneumothorax occurs in the acute pneumonic or caseous type of pulmonary tuberculosis. It never occurs in the fibroid form, and no cases have been reported in acute miliary tuberculosis of the lungs.

The subphrenic abscess described by Leyden may closely simulate pneumothorax, and in some instances the cavity may present every physical sign, although the heart and liver are usually drawn toward the affected side.

The results of pneumothorax may be divided into immediate and remote. They depend, especially at first, upon the condition and more particularly upon the condition of the opposite lung. When the result is not immediately fatal, effusion almost always takes place. The effect in the compressed lung has been held to be favorable. On the other hand, the opposite functioning lung is often observed to become more involved. On the whole, it may be said that pneumothorax is always a serious complication, and with rare exceptions, results in death.

Empyema.—This is seldom met with in pulmonary tuberculosis, and then usually in advanced stages and following pneumothorax, but it is always a serious complication.

Ear.—The close connection between the nose and the ear leads us to the ear in patients with pulmonary tuberculosis is frequently believe that affected. Tuberculosis of the middle ear, more common in males, is rather frequent.

Gastro-intestinal.—Complications occur more frequently in the gastro-intestinal than in any other system. Thrush may penetrate into the glands and form thrombi and metastatic brain abscess. Stomatitis is infrequent in patients with good surroundings. Aphthous ulcers are common. Pyorrhœa alveolaris is frequently seen, and slight gingivitis is not uncommon. Dental caries is frequent and of great importance on account of imperfect mastication, and of infection with tubercle bacilli or secondary organisms. Alveolar abscess is rather frequent.

Tuberculosis of the buccal cavity is of very rare occurrence; the tongue and the tonsils are most often attacked. The tongue, from frequent slight injuries, is rendered more liable to infection, which usually occurs upon its tip or edges. The gums and hard palate are attacked more rarely than the soft palate, uvula, and pillars of the fauces. The posterior pharyngeal wall and the lips are rarely affected. Tuberculosis of the salivary or parotid glands is uncommon.

Gastric Tuberculosis.—Tuberculosis of the stomach, while never primary, is a very rare complication of pulmonary tuberculosis. Various explanations have been offered of its rarity, and Blumer in an excellent *resumé* of the subject concludes that the acidity of the gastric juice in healthy conditions is probably sufficient to prevent the development of tuberculosis, but insufficient if a local point of lessened resistance occurs. Males are more often affected than females. The most frequent site is the pylorus, and the ulcers were multiple in one-half of the cases collected by Blumer. The ulceration often produces remarkably few symptoms, and may be entirely overlooked.

Gastric Ulcer.—Simple ulceration occasionally occurs in pulmonary tuberculosis; 2 instances were found in 1000 cases at the Adirondack Cottage Sanitarium.

Intestinal Tuberculosis.—This is the most frequent of all tuberculous complications in chronic pulmonary tuberculosis, but is rare in the acute forms. It is common only in the more advanced stages, and the great discrepancy which exists between the symptoms in life and the postmortem findings can be explained only by its latency.

The symptoms are notoriously uncertain. Diarrhœa may be absent throughout or alternate with constipation. This depends less upon the extent of the ulceration than upon its site (more pronounced if in the lower colon) and upon the accompanying catarrhal inflammation.

The stools vary greatly in frequency and physical characteristics. Blood in any quantity is rare, but several instances of death from intestinal hemorrhage have been reported. The discovery of tubercle bacilli in the stools is of little value, for in nearly all patients with pulmonary tuberculosis they are present if the sputum contain tubercle bacilli.

Nausea may be present and thirst is often marked. Pain, more often low in the abdomen, is usually colicky and occurs with greatest intensity after food or before defecation. It may be slight or severe and continuous. Chronic diarrhœa in pulmonary tuberculosis is most often associated with intestinal tuberculosis. The most important complications are perforation and stenosis. Tuberculous stenosis of the intestines may occur from concentric hypertrophy in the hypertrophic form or from contraction of scar tissue, formed in a cicatrizing ulcer. The *hypertrophic form* of intestinal tuberculosis occurs chiefly about the ileocecum. The connective-tissue hypertrophy causes a concentric narrowing, although tumors are found at times closely resembling malignant growths. Middle-aged males with slight or slowly advancing pulmonary disease are usually attacked.

Appendicitis.—Simple appendicitis may possibly occur more frequently in patients with pulmonary tuberculosis than in the healthy. It runs its usual course and the same indications for operation exist. Nitrous oxide and oxygen should be used as an anesthetic. Tuberculous appendicitis was formerly considered rare, but has recently been found to be of more frequent occurrence. The symptoms are often so slight and so obscured by the preëxisting pulmonary and intestinal tuberculosis that the appendicular disease is first discovered at necropsy.

Rectal Ulceration.—This is fortunately not common, as it can cause severe pain, both continuous and increased on defecation. If attempts at healing occur, stenosis may result, which, however, is rare, as the condition is usually found only in advanced stages.

Fistula-in-ano.—*Ischiorectal Abscess.*—Fistula is a rather frequent complication, occurring in about 3 per cent. of all cases. It rarely occurs in early life, is uncommon before twenty, most frequent from twenty to forty, and is by no means rare in senile tuberculosis. It may first call attention to the pulmonary disease, or it may, as is more usual, occur in advanced stages associated with ulceration of the rectum. The onset is usually with a perineal or ischiorectal abscess, which (when incised)

fails to heal. The chief symptoms are: severe pain, especially on coughing and on defecation, but after free drainage is established the symptoms may be so slight as to escape the patient's notice. Many of such fistulæ have no discoverable opening into the rectum. In early cases a fistula may exist and cause little or no trouble, and in some cases may precede the pulmonary symptoms by years.

Peritonitis.—Acute peritonitis follows most often acute appendicitis or perforation of a tuberculous ulcer. Peritoneal tuberculosis is infrequent in pulmonary tuberculosis, and most often consecutive to some abdominal complication, *e. g.*, tuberculosis of the mesenteric glands, of the intestine or of the Fallopian tubes.

Circulatory System.—Heart.—The coincidence of pulmonary tuberculosis and heart disease, formerly regarded as rare, is now known to occur in about 1 per cent. of all cases of pulmonary tuberculosis. Acute endocarditis occurs in 5 per cent. of the cases of pulmonary tuberculosis. Tuberculous endocarditis is exceedingly rare.

Mitral insufficiency is the type most frequently found in pulmonary tuberculosis, as the age incidence is more nearly similar. It is said not to predispose to pulmonary tuberculosis, and, if the compensation be good, may exert no unfavorable influence upon the pulmonary disease, and may even retard it. Mitral stenosis was held with some reason to be distinctly inhibitory to pulmonary tuberculosis, which is usually of an abortive form. The prognosis is good. Aortic insufficiency is much less apt to be found with active than with healed pulmonary tuberculosis. Pulmonary stenosis, always congenital, is commonly agreed to predispose to pulmonary tuberculosis, which, however, may develop slowly, although it is frequently miliary (Fox). Tricuspid insufficiency is rare, but may be a great source of danger in benign chronic cases with sclerosis.

Hypertrophy or dilatation of the right ventricle, especially in patients with pleural thickening and shrinking, is not infrequent (Bohland). It is difficult to detect by percussion, but the orthodiagraph often shows it clearly. It is evidenced, also, by epigastric pulsation and accentuation of the second pulmonic sound. The reserve force of such a heart is slight, and dyspnœa and a rapid pulse follow forced exertion.

Pericarditis.—Tuberculous pericarditis usually secondary, and often overlooked, is not common. It may arise from direct extension from the pleura or from perforation from a tuberculous cavity. It occurs in children more frequently than in adults and in men more than in women. The course tends to be chronic. Non-tuberculous *myocardial* degeneration is not rare. Brown atrophy and fatty degeneration are the most frequent forms of all cardiac complications. Myocardial tuberculosis is very infrequent and is often secondary to tuberculous pericarditis.

Arteries and Veins.—Embolism rarely occurs and is recognized in the lungs only when a hemorrhagic infarct forms. Thrombosis is not uncommon, occurs more frequently in the veins, and usually when cachexia is marked.

Anemia.—Pernicious anemia and leukemia rarely coexist with pulmonary tuberculosis. In the former the blood picture may improve as

the tuberculosis grows worse (Erhlich), and pulmonary tuberculosis occurring as a complication of leukemia may essentially modify the blood findings.

Chlorosis.—Chlorosis and pulmonary tuberculosis are so frequently found in the same patient that many declare that chlorosis is but an early symptom of tuberculosis (Landouzy, Labbe).

Nervous System.—Meningitis.—Tuberculous meningitis, always a terminal complication, occurs in about 8 per cent. of all cases. All the symptoms of meningitis can occur and at postmortem no gross lesions be observed. Spinal meningitis can occur alone as well as cerebral (basilar), but is rare and almost always exists in the cerebrospinal form as meningomyelitis.

Genitals.—Tuberculosis of the genitals is not common in pulmonary tuberculosis, but when it occurs is most frequent in the testicles and Fallopian tubes.

Urinary Organs.—Secondary tuberculosis in the genito-urinary system, apart from the kidneys, rarely occurs in pulmonary tuberculosis (Krzywicky places it at 5 per cent.).

Nephritis.—The frequency of nephritis varies much with different observers. Recent careful clinical observation has revealed much more frequent changes than were formerly suspected. The nephritis may affect the symptoms of the primary disease to a certain extent. The temperature may become lower, the pulse faster, and the blood pressure higher. The specific gravity of the urine is high and a few hyaline and granular casts are nearly always present. The symptoms, however, may disappear for several months. Albuminuria is not always present even when extensive lesions exist in the kidneys. Renal complications are usually insidious in their onset and slow in their course. Cardiac hypertrophy is unusual. Pain or aching in the lumbar region, albumin in the urine, œdema, and looseness of the bowels, which may alternate with constipation, as well as unusual fatigue upon slight exertion, unaccountable dyspnœa, and rapid pulse may occur (Walsh).

Albuminuria.—This is rare in incipient pulmonary tuberculosis. It was present at some time after repeated examinations in 62 (5 per cent.) of 1214 patients in all stages at the Adirondack Cottage Sanitarium and is not always present in tuberculous nephritis. Always of unfavorable prognostic significance, it demands cessation of treatment of the pulmonary tuberculosis only when pronounced. Albumoses are said to have been found in the urine of patients who after vigorous exercise suffer from fever (Ott). Their presence has been suggested as a contra-indication for exercise, but is of little value.

Pulmonary Tuberculosis in Nephritis.—Pulmonary tuberculosis occurs in nephritis as frequently as nephritis is found clinically in pulmonary tuberculosis. Secondary tuberculosis may run a slow course in chronic nephritis and the fibroid type is common. In amyloid disease of the kidney 37 per cent. are said to have had pulmonary tuberculosis. Senator finds that in Berlin chronic parenchymatous nephritis is due more frequently to tuberculosis than to any other chronic disease.

Cutaneous System.—The skin frequently presents changes, which, however, are rarely of a tuberculous nature. Chilblains occur frequently and the tendency to a vascular paresis present in many cases no doubt favors the development of erythema pernio.

Purpura hemorrhagica rarely occurs, but a fatal case has been reported. But 3 well-marked cases of purpura have occurred in the last 1000 cases at the Adirondack Cottage Sanitarium. One was a typical case of Henoch's purpura in a man of thirty-one; another was associated with joint symptoms. Herpes zoster is not uncommon.

Tinea or pityriasis versicolor occurs in about 5 per cent. of favorable cases. Various forms of erythema have been described. A macular form is more common in acute tuberculosis and the other forms are rare. Lupus occurs very rarely as a complication of pulmonary tuberculosis, in 6 (0.08 per cent.) of 7485 sanatorium patients collected by Sallis; tuberculous warts (verruca necrogenica) are of extreme rarity.

Lymphatic Glands.—In chronic pulmonary tuberculosis old cicatrices in the neck are not rare. Enlargement of the cervical and axillary glands does take place in a few cases, and in some the glands break down and suppurate, although usually they are just palpable and remain unchanged. In some instances the pus may be loaded with tubercle bacilli. Enlarged tracheal or bronchial glands may cause symptoms referable to compression. The physical signs of enlarged bronchial glands, usually more evident in children, are rarely well-marked in adults. The symptoms may all subside, or suppuration or resolution occur.

Thyroid Gland.—This is frequently slightly enlarged and symptoms suggestive of hyperthyroidism are not infrequent, especially in women. Tachycardia may be pronounced.

Mammary Glands.—Hypertrophy may occur, but is unusual, and is more frequent in men.

Superficial Thoracic Abscess.—Superficial cold (tuberculous) abscess of the thorax is not common in pulmonary tuberculosis. It is usually connected with tuberculous osteitis of the ribs or sternum, or arises from the pleura or lung, but in some instances lies deep under the pectorals and seems to be primary in the muscle. At times these abscesses closely simulate a pointing empyema. In rare instances a cavity may ulcerate through the chest wall and be mistaken for empyema.

Amyloid Disease.—When it occurs it usually affects several organs simultaneously, particularly the spleen, kidneys, intestines, liver, and stomach. Amyloid disease is said rarely to curtail life.

Diabetes Mellitus.—This is frequently complicated by pulmonary tuberculosis, which runs a fatal and usually acute course. It is exceedingly rare for diabetes mellitus to occur in pulmonary tuberculosis. Hemoptysis is rare; the sputum may contain sugar, the sweats are less abundant and the temperature less elevated in pulmonary tuberculosis when associated with diabetes mellitus. Diabetes insipidus occurs very rarely in tuberculosis.

Carcinoma.—The age incidence and the localization of the two diseases are so different that any apparent antagonism is easly explained (Mock). Schwalbe has reported three cases of cancer developing in the wall of

a tuberculous cavity, and Claude thinks that tuberculosis is not uncommon in cancerous deposits. A study of Riffel's monograph upholds the view that pulmonary tuberculosis is not more common in individuals with cancerous antecedents.

Syphilis.—A history of syphilis is not uncommon in patients with pulmonary tuberculosis. The lues is more frequently contracted first, and no doubt often plays an important part etiologically in regard to the pulmonary tuberculosis.

Vaccination.—It is well to avoid vaccination if possible in the advanced stages, and safer in all cases where practicable to isolate the pulmonary patients. In the incipient stage little effect may be noticed.

Diphtheria.—The age incidence of diphtheria and the comparative rarity of the exposure of consumptives to the disease no doubt account for their infrequent coexistence. The patients should be kept in bed out-doors, and antitoxin used as in ordinary cases. In an institution, prophylactic doses of 500 units should be repeated every two weeks as long as necessary. Caution is necessary when the pulmonary tuberculosis is complicated by enlarged lymph nodes.

Rheumatic Fever, etc.—Patients with pulmonary tuberculosis rarely have rheumatic fever. Indefinite pains in the joints are common, myalgia not infrequent, but swollen, painful joints are rare. West thinks an antagonism exists between the two diseases. The writer has seen but 1 instance in 2000 cases. Gout is rarely seen with pulmonary tuberculosis, and some antagonism is said to exist between them. The age incidence is also different. Furthermore the gouty are well nourished and have a vigorous constitution. Poncet has recently called attention to a tuberculous arthritis which occurs in tuberculous patients and often results in ankylosis. It is most frequent in children between seven and twelve years of age. It is distinguished from rheumatic fever by its mode of onset, by the slight general and predominant local symptoms (persisting in the joint affected), by the inefficiency of the salicylates, and by infrequency of cardiac complications. Arthritis deformans of the spine may occur in connection with pulmonary tuberculosis, and suggest tuberculous spondylitis.

Addison's Disease.—This is a rare complication and only 2 patients out of 2600 at the Adirondack Cottage Sanitarium are known to have had the disease.

Pregnancy and Parturition.—Pregnancy often occurs in pulmonary tuberculosis. Bacon has recently pointed out that pulmonary tuberculosis is at least as frequent in pregnant women as in the general population. From 1 to 1.5 per cent. (about 30,000 in the United States) of all pregnant women may be said to have a discoverable tuberculous lesion (Bacon), and West states that pulmonary tuberculosis is more prevalent among married than unmarried women.

The effects of pregnancy and parturition upon pulmonary tuberculosis are to be separated. Pregnancy, if it causes no nausea or vomiting, often seems to exert little if any influence upon the pulmonary disease. In a few cases the disease is apparently arrested and the nutrition and general and local condition of the patient are much improved during the

pregnancy. In acute progressive cases pressure of the enlarged uterus may cause discomfort and dyspnœa; the cough and fever may produce abortion, which, however, occurs far less frequently than in heart and kidney disease. Conception can occur at almost any stage of pulmonary tuberculosis.

The effects of parturition, although it lasts but five or six hours, are always to be regarded seriously. It is well recognized that after labor or abortion the pulmonary tuberculosis may run a rapid course. This is more often so if tuberculous laryngitis is present. The prolonged muscular exertion, the loss of blood, the attendant exhaustion, and the possibility of the inhalation of infectious material are always serious. The apparent indifference of many physicians to these facts is astonishing.

Pregnancy (including labor) may awaken old, quiescent lesions, and incite fresh ones to renewed activity. In advanced cases pregnancy is always serious, and, when laryngeal lesions are present, the mortality is said to be 61 per cent. (Fellner). Multiple pregnancies even in cured patients are dangerous.

DIAGNOSIS OF TUBERCULOSIS

In no disease is diagnosis more important, for it has been clearly shown that not only the immediate, but the permanent results of treatment are closely connected with and dependent upon the stage of the disease in which the diagnosis is made. He who always waits for tubercle bacilli to appear in the sputum before making a positive diagnosis is apt to come to the conclusion that many cases of pulmonary tuberculosis have slight chances of recovery. Personal acquaintance with a patient or his family should have no negative value in diagnosis.

Source of Infection.—The discovery of a source of possible infection is an important point that needs careful investigation. This is the most important information to be gleaned from the family history, and a mere enumeration of the deaths occurring in the family from pulmonary tuberculosis, without exact details of the contact of the patient with the afflicted members is of small value. The habitation, workshop or office, and particularly the fellow-lodgers or employees, should be recalled by the patient to trace a likely source of infection. This is, if present, valuable in diagnosis, but its absence is of no great importance.

Predisposing Factors.—Due regard should be paid to the occupation. Great mental anxiety, grief, worry, care, frequent parturition and prolonged lactation, abuse of stimulants, excess in venery, insufficient food, exposure to cold, unsanitary surroundings, and such diseases as measles, whooping cough, and smallpox, are all of importance. A history of previous adenitis or joint disease is of much value.

Symptoms.—In many instances these play a very important part in diagnosis and appear almost invariably before physical signs are manifest in the lungs. Many patients lose their chances of recovery by the dilatory practices of some physicians. Suspicious symptoms should put us on our guard, and after due consideration, if explained fully in no other way,

steps to be mentioned later should be taken at once to settle definitely the diagnosis. The localizing symptoms, such as hemoptysis, cough, and pleurisy, have greater diagnostic value than general symptoms such as rapid pulse, fever, loss of weight and strength. When two or more are combined it is suggestive of tuberculosis, and if associated with hemoptysis it is sufficient to subject a patient to treatment. Any of these symptoms following measles or whooping cough are always of grave import. Persistent, obstinate hoarseness or the history or presence of ischiorectal abscess or fistula always suggests a careful pulmonary examination, even if only slight symptoms are present. Preëxisting tuberculous lesions indicate a similar course. A combination of loss of weight and strength, fatigue after slight exertion, and loss of appetite, are usually embraced in the term "run down," and together with a slight cough form one of the commonest onsets. Stiffness and pain in the joints are sometimes present early. Oppression under the sternum, sometimes quite marked, and indefinite pains in the chest, especially between the scapulæ, are far from rare. The menstruation may be early affected, and later may entirely cease.

Fever.—The bodily temperature plays an important part in diagnosis. Exercise readily causes a rise of temperature (Penzoldt's reaction) in tuberculous patients, but must be made use of very carefully when diagnosis is doubtful. The patient may be kept quiet for three or four days, then allowed exercise. A comparison of the temperatures during the two periods may aid greatly in the diagnosis, but other debilitating diseases may act in a similar manner (Burton-Fanning). In healthy women the temperature of the premenstrual period not infrequently reaches 99.5° or higher. In some nervous or fat individuals, as well as during convalescence from infectious fevers, the temperature may be very easily elevated.

A persistent slight elevation of temperature without apparent cause is a very suspicious symptom, and should always be fully investigated. In a number of cases a persistent afternoon temperature of 99.5° to 100° is the earliest symptom. Disturbed sleep and a slight tendency to sweat may be the only signs of fever.

Loss of Weight.—This occurs in the majority of all patients. It is a striking fact that at the Adirondack Cottage Sanitarium the average weight of the patients on discharge, after an average gain of about 14 pounds, and while considerably above their weight in health, is no more than it should be normally. In other words, the consumptive is a person whose weight in health is considerably below the normal.

Loss of Strength.—Loss of strength, usually insidious in its onset, may first attract the patient's notice but other causes of general weakness, must be excluded. Slight loss of strength, especially when coupled with localizing symptoms, is, at least, suggestive.

Cough.—This is the most frequent early symptom and nearly always the one which first draws attention to the lungs. A slight persistent hacking cough, often dry at first, and occurring possibly only after a deep breath, should receive careful attention. It often has periods of marked remission, so that the patient believes he is recovering from the

"cold," and may give a history of "colds," repeated over a long period. A summer cough is always more suspicious than a winter cough.

Hemoptysis.—In nearly all cases a period of more or less pronounced ill-health precedes the so-called primary hemoptysis. The first point to be considered is the source of the blood. Blood from the nasopharynx may be mixed with mucus, but usually some epistaxis is present. It may come from varicose veins at the base of the tongue or on the posterior pharyngeal wall. Bleeding from the larynx, unless it is seriously diseased, is of such rare occurrence that it need not be considered. A careful examination of the mouth, nose, and throat should always be made if any doubt exists. The amount of blood from these sources, when there is no epistaxis, is usually slight. It is rare for a hemorrhage of over one ounce to come from elsewhere than the lungs, stomach or, nose. Slight blood-spitting following cough on several successive mornings is characteristic of hemoptysis of tuberculous origin. It is rare in pulmonary tuberculosis to have a brisk hemoptysis not followed by blood-stained sputum for a day or longer.

The bloody sputum should be fully examined. A uniform pink or bright red, watery fluid, consisting almost entirely of saliva, comes usually from the gums or mouth and may be present for months. It should not be confused with wine, tobacco, prune juice, licorice, or medicine. Streaks of blood upon the mucus or upon masses of sputum usually come from the bronchi, and are not uncommon in bronchitis after severe coughing. Uniform pink, red, rusty, or darker (prune juice) viscid pellets, containing minute air bubbles, occur in pneumonia (most common), heart disease, and pulmonary tuberculosis. Small purple or dark lumps without air bubbles which sink in water are usually due to heart disease. Pure blood in some amount, if it is frothy, is usually from the lungs, trachea, or bronchi, and if mixed with mucus or pus is unquestionably from the lungs. The blood of hemoptysis may be swallowed and then vomited.

When it is determined that the source of the blood lies below the larynx the next step should be to exclude all extrapulmonary disease which might cause hemoptysis. Among these are ulceration of the trachea (rare), heart disease, aneurism, certain diseases of the blood (purpura, hemophilia, scurvy, leukemia, pernicious anemia, the malignant type of some infectious fevers), atheroma of the pulmonary vessels, and abscess of the liver (perforating through the lungs).

Having excluded all sources of the hemorrhage except the lungs, these organs should receive due attention. At least 90 per cent. of all patients who have hemoptysis develop at some later time pulmonary tuberculosis. Absence of physical signs is no proof of a non-tuberculous origin. Every patient who suffers from hemoptysis of a dram or more without a discoverable cause should be considered tuberculous until it is proved otherwise. The blood, and particularly any particles of pus or mucus, should always be examined for tubercle bacilli, which are found in a number of cases. The examination of the blood of hemoptysis for tubercle bacilli may be greatly facilitated by hydrohemolysis, the addition of 12 to 20 volumes of water or of one-third volume of alcohol to the blood before centrifugalization. Slight general and local symptoms with an

undoubted history of hemoptysis justify a diagnosis of tuberculosis. Every patient who has suffered from hemoptysis and in whom a definite diagnosis cannot be made should eventually be given tuberculin. Hemoptysis may occur in bronchitis (especially fibrinous), bronchiectasis, gangrene, abscess, asthma, emphysema, acute lobar pneumonia, infarct, embolism, anthrax, syphilis, actinomycosis, parasitic diseases (echinococcus, distomum), tumors (carcinoma, sarcoma), in trauma of the lung or air passages, and in fact to a slight amount in nearly every pulmonary disease. The physical signs in these cases are usually well-marked, and, furthermore, hemoptysis in them is of rare occurrence. Several observers have described a "nervous" hemoptysis in the hysterical, but without tuberculin such a diagnosis cannot be made. Vicarious menstruation has rarely been proved to occur in normal lungs.

Dyspnœa.—Shortness of breath is sometimes the first symptom noticed by the patient, but it rarely occurs to such a degree that a physician is consulted in regard to it before other symptoms set in. Unaccountable dyspnœa or a sudden attack of asthma is always suspicious.

Pleurisy.—Recent work has done much to prove that most idiopathic pleurisies are tuberculous. If other organic disease can be excluded, the pleurisy should be considered tuberculous until the contrary be proved. A dry pleurisy at one apex or a double pleurisy without other cause is nearly always tuberculous. Even if tubercle bacilli cannot be found in a pleuritic effusion it is well to assume the patient to be tuberculous, and to treat him accordingly. A persistent feeling of pressure in the chest demands careful consideration.

Physical Signs.—The value of physical signs must not be overestimated. When it is recalled that large central lesions can, but rarely do, exist without discoverable physical signs, absence of physical signs is not astonishing. Marked physical signs are not to be expected in early cases, and any change from normal may become evident only after repeated examinations. At least two examinations are necessary before the chest can be said to be normal in regard to physical signs. On the second examination those places should be first examined which were suspicious on the previous examination.

Percussion yields little aid in some patients in early stages, but when the disease is of some duration its value is markedly increased. Slight differences should be checked by repeated examinations and after a full inspiration. Absence of dulness may occur even in advanced cases and hyperresonance should receive careful attention. Emphysematous changes may produce a relatively low note on the affected side. The right apex usually reaches a slightly lower level than the left, a point of no great importance. The movement of the bases of the lungs and the resonant areas above the clavicles must be carefully mapped out by percussion.

Auscultation undoubtedly yields the most trustworthy information and in many early cases it gives the only change in the physical signs. It should be practised before the patient is made to breathe deeply, and on a second examination the auscultation of the suspected area should be the first procedure. Slight changes in the breath sounds at the right

apex are often difficult of detection. They are of more value if detected at only one apex, and if present at both the patient should be made to breathe noiselessly through his mouth, and the presence of stenosis of the larynx or bronchi by pressure from aneurysm, tumor, enlarged glands, or traumatism excluded. Prolonged high or low-pitched expiration, or spluttering of the inspiration, suggesting fine crepitations which, however, cannot be heard, wavy breathing, weakened breathing, are all signs of great importance when limited to one apex. Wavy breathing must be carefully separated from the cardiorespiratory murmur. A venous murmur above one clavicle may suggest loss of vesicular murmur until the patient holds his breath. Some prolongation of the expiration may occur at the right apex in children, in thin, lanky women, and during forced respiration in many individuals. The whisper should *always* be auscultated over the entire chest, as in some instances it will first draw attention to the diseased area.

The change in breath sounds alone is rarely sufficient for diagnosis, but rales persistent or occurring on several examinations at one apex not due to influenza, and coupled with slight symptoms, border on certainty. Rales are more important than dulness and are frequently overlooked through failure to have the patient cough and breathe properly. They may be present one day and absent the next, to recur on the following day. They are more likely to be heard on damp days than on dry, in the morning on waking than during the afternoon. Iodide of potash, certain alkaline mineral waters, tuberculin, and menstruation may increase the rales, while excess of alcohol (Turban), certain drugs (balsam, tars, etc.), profuse sweating, or prolonged dry, following damp, weather may decrease the rales. A sonorous rale ending in a prolonged expiration is almost pathognomonic of pulmonary tuberculosis (Williams). Fine rales may be heard in the prone and not in the upright position, and Upham believes when lying on the affected side rales may be heard that otherwise escape detection. Cybulski's laryngeal crepitations (oral rales) occur usually too late to be of any diagnostic aid.

Extraordinary care must be exercised in differentiating various sounds heard in the normal chest from rales: (1) Skin friction sounds are often heard just after the stethoscope is placed upon the chest, and slight pressure applied to it as the patient begins to inhale. A second breath or cough before moving the stethoscope or dipping the bell in water or vaseline will often eliminate these sounds. (2) The sounds produced in the muscles may resemble a hum, a fine crackle, or, if one muscle slips over another, a snap or friction sound. Such sounds are usually heard on the back, most often on both sides, but may be limited to one, and call for much ingenuity and experience in differentiation from fine rales. (3) A sound produced on swallowing resembling fine rales may cause some confusion, but is easily prevented by a word to the patient. (4) Sounds produced in the stomach and intestines can be heard over the lower part of the lungs and seldom cause error. They are usually heard on the left side below the limit of pulmonary resonance. (5) The peritoneal friction rub is rarely a factor worth considering. (6) The shoulder friction seldom enters into consideration, but may be heard in some

cases over the scapula and shoulder-joint, and at times closely simulate a pleuritic rub. (7) The occurrence of rales in the normal chest is still a mooted point. Atelectatic rales unquestionably occur over the base of the lungs posteriorly, but these quickly clear up. No good proof of rales in the chest of a person in health up and about has yet been presented. In one case where only a few rales existed in the infra-axillary region on one side, the patient reacted to tuberculin, and several years later relapsed and had tubercle bacilli in the sputum.

The location of the physical signs is the most important point in diagnosis. Pulmonary tuberculosis usually attacks the apex first, and persistent physical signs localized in the apex of one lung should always be considered tuberculous until the contrary is proved. The opposite is true of physical signs at the pulmonary base. Primary basic tuberculosis may occur, but basic tuberculosis is usually secondary to an older apical lesion. A secondary tuberculous infection of a non-tuberculous basic lesion may take place.

Scattered rales over a side with bronchophony and without dulness or other signs are nearly always due to tuberculosis (Williams). This is also true of pleuritic friction sounds at one apex or on both sides in the absence of other causative factors. In early childhood the resilience of the chest walls and the dissemination usually render diagnosis from bronchitis or bronchopneumonia difficult. Examination of the stools for tubercle bacilli should be made. In old age prolonged expiration, jerky breathing, and even a few dry rales are of less import than in adult life unless limited in area. Symptoms in these cases are of much importance.

Contraction or atrophy of certain muscles (pectoral, sternocleidomastoid, trapezius, etc.) may at a glance or on palpation suggest disease at one apex.[1]

A change may occur in the frequency of the pulse when the patient assumes an erect posture. The pulse may have a lower tension than normal, but its increased frequency is the most important factor. A persistently high pulse without fever, coupled with loss of weight, is suggestive of tuberculous infection.

Neither physical signs nor symptoms alone are sufficient in many cases for diagnosis; but the combination of slight signs and symptoms will often definitely settle the matter. Slight or indefinite physical signs without symptoms are not sufficient to establish a diagnosis.

Sputum.—The rule to examine the sputum of every patient who has any respiratory affection, slight or serious, admits of no exception. If the patient says he has no sputum, a specimen obtained by clearing the throat in the morning or after meals should be requested. The macroscopic appearance of the sputum is of little if any value, and the absence of tubercle bacilli in the sputum is no proof of the absence of pulmonary tuberculosis. One positive examination settles the diagnosis, but one negative examination is of little value. The presence of elastic tissue in the sputum is evidence of destruction of the pulmonary tissue.

[1] See Pottenger, Muscle Spasm and Degeneration, 1912.

Tubercle bacilli may be absent on repeated examinations when the disease has become fibroid, but the absence of these bacilli when the lung is breaking down or has undergone extensive destructive changes is presumptive evidence that the disease is non-tuberculous. Tubercle bacilli may be found in the sputum months before physical signs appear in the lungs. They undoubtedly find their way into the nasal and buccal secretions and have been discovered there in healthy individuals. For this reason one tubercle bacillus is not sufficient for a diagnosis. In children or in patients who are suspected of swallowing the little sputum they have a careful examination of the vomitus, stomach contents, a swab of the fauces, or of the feces by Strasburger's method (mixing with water, sedimenting, mixing the top layer with three or four parts of 95 per cent. alcohol, centrifuging and staining the sediment) should be made. The expectoration of calcareous matter rarely if ever occurs except in tuberculosis of the lungs or of the bronchial glands. The inoculation of sputum into a guinea-pig will at times reveal tubercle bacilli that cannot be found by careful and repeated examination.

Potassium iodide in some cases undoubtedly increases the bronchial secretions, and in some instances tubercle bacilli while absent previously have been found in the sputum following its administration. When no sputum can be obtained and the patients cough, it has been advised by Blume to have them cough for eight or ten mornings on large slides, which are then stained.

Sputum Examination.—The chief value of this is for diagnosis. Its prognostic importance has been greatly exaggerated and so far no practical method has been devised by which secondary infection can be accurately diagnosed. The diagnosis in most cases should be made before tubercle bacilli appear in the sputum.

The *collection* of sputum for examination is very important. It is surprising how often tubercle bacilli occur in patients who have "no" sputum. The morning sputum should be obtained when possible and the specimen should always be coughed up from below, not drawn down from the nose. Patients with little sputum should be told to bring the little dense, tough balls they raise at infrequent intervals. These are often the only parts of the sputum to show tubercle bacilli, and great stress should be laid on their collection. Tubercle bacilli stain well in putrefying sputum after three months or longer.

The blood of an initial hemoptysis should always be examined for tubercle bacilli, and, if none are found, inoscopy or hemolysis should be carried out. No sputum should be said to be free from tubercle bacilli until it is negative on at least three successive days, and the examiner is convinced that it has been carefully collected.

The *macroscopic* examination reveals in many instances little of value. Sputum in pulmonary tuberculosis has no pathognomonic macroscopic appearance. Early in the disease the sputum is largely mucoid, more or less transparent, and with an occasional fleck of yellow pus. As the disease advances it may become white, contains less air, and finally assumes a yellow or yellowish-green appearance, occurs in masses (num-

mular sputum), and sinks in water. As improvement sets in, the sputum becomes less yellow, then white, and finally consists of glairy mucus, which may persist for months and years. Macroscopic particles of lung tissue are occasionally found in the sputum and usually consist chiefly of elastic tissue. Lung stones are infrequent. The presence of actinomycotic grains should be excluded.

Quantity.—This varies from the slightest trace to 800 cc. in twenty-four hours, but rarely exceeds 100 to 125 cc. a day. As a rule, in the earlier cases the sputum is small in amount, increases as the disease advances, and is seldom absent when symptoms have continued for two months or longer. While the disease is undergoing arrest, the sputum usually diminishes and finally disappears. Sudden changes in the amount call for a careful examination, as a sudden decrease sometimes occurs in acute miliary tuberculosis and has been observed in temporary heart weakness or intercurrent diseases. Miliary tuberculosis is at times ushered in with a sudden increase of the sputum. In many cases the morning sputum is the first to appear and the last to disappear.

Consistency.—This varies from that of water to sputum so tenacious that it will remain in an inverted cup. The sputum ordinarily is moderately tenacious.

Lung Stones.—Chalky concretions are usually found in the sputum of chronic patients with rapidly advancing ulceration. Kidd believes that they are nearly pathognomonic of pulmonary or glandular tuberculosis. They are rather uncommon (16 among 1000 cases, Williams), and usually occur singly from time to time (500 from one patient).

Their size varies from that of a small shot to one as large as a cherry, so large it caused suffocation in a child. They are generally very irregular in form, with numerous rough projections and usually white. They are formed in the lungs and glands from calcification of caseous masses, and it is said "in obstructed bronchi," but this is to be questioned. They may occur at the time of hemoptysis.

Variations According to the Type of the Disease.—In acute pneumonic phthisis the sputum is at first similar to that of acute pneumonia. Later it takes on a greenish tinge. Such a change in an unresolved pneumonia is always suspicious. Acute miliary tuberculosis of the lungs may occur without sputum. If secondary its onset may be marked by a sudden diminution of the sputum or by a change to a watery consistency and a marked increase in the amount. An attack of acute bronchitis may decrease the sputum temporarily to increase it later.

Microscopic.—The examination of a fresh specimen may prove to be of value and reveal elastic tissue. In every case where tuberculosis is suspected from the symptoms and physical signs and no tubercle bacilli are found, careful examination of the fresh sputum should be made.

Selection of Particles.—Search should be made for the little flecks of pus or cheesy particles which are readily seen on a black background. The wooden specimen box, painted black, is excellent (Hart). Each slide or cover-slip should contain particles from five or six different parts of the specimen.

Cells.—The cellular elements of the sputum include pavement epithelium, alveolar, ciliated, glandular, cylindrical, pus, red blood, and giant cells. In some cases the cells may be pigmented.

Elastic Tissue.—Dettweiler's maxim, "Where elastic tissue is, there are also tubercle bacilli; indeed, the greater the number of fibers, the more numerous the tubercle bacilli," is still held in part, but its converse cannot be affirmed, as many specimens contain tubercle bacilli and no elastic fibers. Tubercle bacilli always occur first. Elastic fibers are the surest sign of extensive destruction of pulmonary, bronchial, or tracheal tissue. Their constant presence shows advancing disease. They are absent in acute processes until the walls of the bronchi are broken down; 90 per cent. of all cases in which elastic tissue occurs are said to be tuberculous. Elastic fibers may occur for one or two years without signs of cavity formation.

Various crystals may be found in tuberculous sputum, and among them may be mentioned Charcot-Leyden, cholesterin, hematoidin, fatty, leucin, tyrosin, phosphate, and oxalate crystals. Fibrinous coagula, striking tree-like bodies, may occur in phthisis as well as in fibrinous bronchitis. Casts of the bronchi also occur, and it is not very rare to find the blood coagulum after an hemoptysis in the form of a cast of a bronchus. Caseous matter may be found.

Tubercle Bacilli.—The search for tubercle bacilli in the stained specimen is unquestionably the most important step in the examination of a suspected person. The stain consists of 1 part of saturated alcoholic (95 per cent.) solution of fuchsin and 9 parts of 5 per cent. carbolic acid solution. Many new stains have been introduced, but none have stood the test of time like this. Either cover-slips or slides may be used, but on the whole slides are more satisfactory. Only new slides or slips should be used in specimens for diagnosis. The time required for staining varies with the degree of heat employed; the greater the heat to a certain point, the more rapid the staining. A small flame should be used, and the fluid brought just to a boil, or, better, until bubbles are seen to collect about the thicker parts of the smear. This heat should be kept up for one to five minutes, or until crystals of fuchsin are seen to appear on the surface of the fluid. In routine work much time is saved by using the "cold" method. This consists in immersing the preparations in the cold stain for twenty-four hours.

Decolorization.—Alkalies, other dyes, salts and alcohol, as well as acids, organic and inorganic, can decolorize specimens. Acid alcohol and Ebner's decalcifying fluid (HCl, $NaClO_3$, of each 2.5 parts dissolved in 100 parts of distilled water and 500 parts of 95 per cent. alcohol added) are excellent. (Tubercle bacilli resist this for ten or more minutes.)

The tubercle bacilli are to be well stained in the first place and then carefully decolorized, controlling this step in important cases by frequent examinations under the low power of the microscope. This cannot be done if a counter-stain is added to the decolorizing agent, and, therefore, Gabbett's solution (2 per cent. methylene blue in 25 per cent. H_4SO_2), so widely used, should never be employed for diagnosis nor in any case for urine. For routine examinations in sanatoriums the use of Gabbett's

solution is permissible after diagnosis, but is not to be recommended, as every specimen should be subjected to alcohol and counter-stained later with methylene blue.

Differential Diagnosis from Other Acid-fast Bacilli.—The important point in the differential diagnosis of the tubercle bacillus lies in its resistance to decolorization not only by acids, but by alcohol. A large number of "acid-fast" bacilli have been found, but so far none resists alcohol to the same extent as the tubercle bacillus. The only absolutely certain method is to control the decolorization by subjecting tubercle bacilli placed on the same cover-glass or slide to exactly similar manipulations. The majority of the acid resisting bacteria grow readily and quickly on the usual media, often at room temperature. Inoculation of guinea-pigs may have to be employed. In most instances these bacilli differ morphologically from the tubercle bacillus, and are usually longer or shorter and broader. They occur in butter, milk, smegma, contents of tonsillar crypts, cerumen, nasal secretions, in the sputum of some cases of gangrene, bronchiectasis, and putrid bronchitis, in manure, and on timothy hay.

Examination.—This should be done systematically and thoroughly with a mechanical stage, and at least two preparations from each specimen should be examined. Much time can be wasted by counting tubercle bacilli in the preparations, but a schema such as that devised by Gaffky is of considerable value in comparing the findings from time to time. It is as follows:

1. Only 1 to 4 bacilli in whole preparation.
2. Only 1 bacillus on average in many fields.
3. Only 1 bacillus on average in each field.
4. 2 or 3 bacilli on average in each field.
5. 4 to 6 bacilli on average in each field.
6. 7 to 12 bacilli on average in each field.
7. Fairly numerous on average in each field.
8. Numerous on average in many fields.
9. Very numerous on average in many fields.
10. Enormous masses on average in many fields.

In this method a No. 3 ocular with 16 mm. tube length and $\frac{1}{12}$ oil-immersion lens should be used. The fallacy of basing any conclusions upon the number of bacilli is readily seen when the uncertain distribution of bacilli in the sputum is kept in mind. A number of methods have been devised to determine accurately the number of bacilli, but they are of little practical value.

A careful study of the sputum of 259 cases at the Adirondack Cottage Sanitarium showed that when the diagnosis was made before tubercle bacilli were present in the sputum, *i. e.*, before ulceration had begun, the chances for recovery were at least twice as good and on the whole seemed many times better; that only 44 per cent. of the patients with tubercle bacilli on admission had lost them on discharge after a residence of about five months; that the number of bacilli seems to vary on the whole directly with the severity of the case; that if the number of bacilli steadily decreases in a series of examinations at intervals sufficiently long, the

patient may be improving, but the constitutional symptoms and local signs are much more trustworthy; that if on repeated examinations large numbers of bacilli are found, the disease has in all probability advanced to cavity; that the morphology of the tubercle bacillus affords little or no ground for prognosis, but the short bacilli are suggestive of a more active process; and that the arrangement of the bacilli in clumps may occur in all, but is more apt to be found in the severer cases.

Splitter sputa, fine, generally long granules, arranged in a row or in groups, Spengler believes are involution forms of tubercle bacilli and may be found when no "normal" tubercle bacilli can be seen. Such sputum is not always infectious to guinea-pigs. Much's granules are of little diagnostic aid in sputum. The tubercle bacilli usually occur free, but may be found in pus or alveolar cells.

Secondary Organisms.—It can be safely said that a diagnosis of secondary infections, on account of the rapid growths of these organisms, cannot be made from sputum examined several hours after expectoration. The mouth should be thoroughly cleansed before collecting the specimen and the sputum, not later than fifteen minutes after it is expectorated, should be carefully washed in three to ten changes of salt solution. The mass should then be torn apart and a piece of sputum from the middle of the mass examined. Secondary infection should be diagnosed only after repeated examinations, and even then so many errors may creep in that clinical symptoms have often to be relied upon.

In the ordinary examination of sputum, streptococci, staphylococci, diplococci, torulæ, sarcinæ, and bacilli, singly, in chains, or in zoöglea masses, occur more or less frequently. A biscuit-shaped diplococcus resembling the gonococcus is common. The pneumococcus and Freidländer's bacillus are less frequent.

Methods for Increasing the Number of the Tubercle Bacilli in the Part of the Specimen to be Examined.—When no tubercle bacilli can be found in a suspected case various methods have been devised to make the search more accurate. The one most frequently employed is to render the sputum more or less homogeneous and then to sediment or centrifugalize it. Antiformin, best prepared by mixing, just before use, equal parts of Javelle water and 15 per cent. sodium hydrate, is an excellent solvent for the sputum. After treatment the sputum can be centrifugalized and examined. Digestion of sputum for twenty-four hours in the thermostat, by the addition of one-half volume of a 0.6 per cent. sodium carbonate, followed by centrifugalization, and the further addition to the sediment of four volumes of 0.25 per cent. sodium hydrate, followed again by centrifugalization, yields excellent results. Digestion with pancreatin in a slightly alkaline solution for twenty-four hours or longer yields good results. Vigorous shaking with 9 parts of 5 per cent. carbolic acid solution and 1 of sputum, followed by centrifugalization or sedimentation, is useful. A fixative such as egg albumen or some of the original sputum must be used with these methods. Inoscopy has been successful in some cases.

Another procedure which has given less satisfactory results is the "enriching" of the specimen. In ordinary sputum at room temperature

or even in the thermostat, little or no evidence of increase of the tubercle bacilli can be found. The addition even of some culture medium to the sputum seems to aid little in the growth of the tubercle bacillus. Making a culture from the interior of a piece of sputum thoroughly washed, on blood serum or brain agar, or planting first on gelatin plates and then replanting on blood serum from parts of the plate apparently sterile, may aid in diagnosis. Dilute formalin affects the growth of acid-fast bacteria less than that of some other forms. An emulsion is made of the sputum and a few drops of formalin added. At different intervals beginning at ten minutes, tubes are inoculated and pure cultures of the acid-fast organism may be obtained in some. A marked increase in the number of these organisms at 30° C. in ordinary bouillon is conclusive proof that the organism is not the tubercle bacillus.

Several years ago Strassburger suggested in the examination of the stools for tubercle bacilli, diluting and sedimenting first with water and then with alcohol. This decreases the specific gravity of the fluid and so hastens sedimentation.

Injection into Animals.—Sputum in which no tubercle bacilli can be found, which on inoculation produces no tuberculosis in four to six weeks, contains no tubercle bacilli. The sputum should be injected, as soon as possible after it has been collected, subcutaneously in the groins of two guinea-pigs and the animals examined from time to time for enlarged inguinal lymph glands. At the end of four to six weeks the animals should be given an intradermic tuberculin test and killed and any enlarged glands thoroughly examined for bacilli or for tubercles, both macroscopically and microscopically. Intraperitoneal inoculation is thought by some to be more sensitive than subcutaneous. Nattan-Larrier advises inoculation into the mamma of a guinea-pig, one or several days after delivery. Tubercle bacilli are said to occur in the milk on the fifth to the tenth day. Heating the sputum to 60° C. for ten minutes may destroy many secondary organisms which may be virulent for the guinea-pig without affecting the tubercle bacilli. Pseudotubercle bacilli can produce tubercles, but cultures readily separate the two forms. To attempt to determine the virulence of a strain of tubercle bacilli by injection of animals with sputum is futile, unless the number of bacilli in the injection can be controlled.

Urine.—The urine is of slight value in diagnosis. Albuminuria is exceedingly rare in incipient cases. Polyuria is uncommon.

Cytodiagnosis.—It has been suggested to blister and to examine the exudate. If the eosinophiles in a differential count fall much below 8 per cent., pulmonary tuberculosis is said to be suggested.

Tuberculin.—Tuberculin should be used diagnostically only as a last resort. In brief, if we except leprosy, for the time being, tuberculin is a specific test for the detection of tuberculous infection. The danger from the use of the tuberculin test is slight, but in some unsuitable cases very real and possibly severe. Reaction, even when severe, has no connection with the appearance of tubercle bacilli in the sputum. Increase of physical signs occurs in about one-third of all the cases and in one-half of those with increase of pulmonary symptoms, and is inde-

pendent of the appearance of tubercle bacilli in the sputum. In practice, exposure to infection, characteristic symptoms, such as hemoptysis, pleurisy with effusion, dry pleurisy on both sides, and localized persistent physical signs at one apex, are diagnostic data of far more importance in clinical tuberculosis than those derived from the tuberculin tests. A positive reaction, when only doubtful symptoms of pulmonary tuberculosis are present, is of uncertain value unless the pulmonary symptoms or signs are definitely increased during the reaction. A negative reaction is of uncertain value, and in the face of positive symptoms carries little weight. In many instances the tuberculin tests only add confusion to the clinical data. The subcutaneous test, depending as it does upon the reaction at the site of the lesion, is still the most reliable of the tuberculin tests; but neither this nor any one of the modifications as yet devised, clearly differentiates clinical tuberculosis which demands vigorous treatment from non-clinical tuberculosis which requires only a God-fearing life.

The best variety for diagnostic purposes is the old or original tuberculin of Koch. Its strength is far from constant even when prepared by the same method and from the same strain of tubercle bacilli.

Subcutaneous Methods.—Dosage.[1]—The dose necessary to produce a reaction in a healthy individual varies considerably with the tuberculin used: 0.01 cc. of the original tuberculin rarely produces a typical reaction in a normal person. For an adult 0.0005 cc. is a safe initial dose, but in many cases it is not necessary to give less than 0.001 cc., although it is often best to give first 0.0001 or 0.0002 cc. If no reaction occurs the following doses should be given: 0.001, 0.005, and 0.008 or even 0.01 cc. It is well always to repeat the last dose. Some advise a single large dose for fear that repeated small doses may produce some immunity, and affirm that no higher reactions occur in a susceptible individual from a dose of 0.005 to 0.010 cc. than from 0.001 or 0.002 cc. The observations of the writer do not bear this out.

The general condition and build of the patient, together with the duration and extent of the disease, must be considered in the dosage, as well as the age in children. In children, 0.0001 cc. is a safe initial and 0.003 cc. a safe maximal dose. Loewenstein recommended the use of small doses, 0.0001 cc., or 0.0002 cc. repeated three or four times. From a limited experience with this method it would appear that patients who react suffer as severely as those who are given larger doses, and the fact that the larger doses must in some cases be eventually administered prolongs the test considerably.

Method of Administration.—In order to measure the dose, the tuberculin must be diluted, preferably by the physician. This is best done by means of a pipette, graduated to read to hundredths of a cubic centimeter, and a graduated cylinder. A solution of 0.25 per cent. phenol in physiological salt solution is the best diluent, but either may be used alone. The phenol solution may be kept one week in a dark, cool place,

[1] In O. T. and B. F. 1 cc. = 1 gram; in B. E. and T. R. the dose is stated in amounts of the solid substance.

but a solution in normal saline should be freshly prepared for each injection. The hypodermic syringe should be carefully sterilized, preferably by boiling, as well as all pipettes and cylinders. It is sufficient to cleanse the skin thoroughly with 70 per cent. ethyl alcohol before and after the injection, which is best made subcutaneously in the subscapular region, avoiding areas of induration produced by previous inoculation. The reaction usually occurs in eight to twenty hours, and it is well to administer the tuberculin during the evening or late afternoon. It may occur earlier (in four hours) or later (in thirty-six hours), and possibly, if very slight, be obscured by sleep, but this must be of rare occurrence. The temperature of a patient should be taken every two hours while awake for several days (at least two) before the tuberculin injection.

The patient should be kept quiet but not necessarily in bed. The main advantage of rest is the avoidance of every possible cause that may influence the reaction. Theoretically the patient should be under the same conditions before and during the test. The temperature should be recorded for two or three days after the reaction. If the patient fails to react, the second dose should be given two to four days later, and the other doses repeated at the same interval.

Contra-indications.—Tuberculin should not be used when a patient's oral temperature reaches 100° at any time of the day. In patients with extensive physical signs it should be employed with the greatest care. It should not be administered to patients with night-sweats, great dyspnœa, recent hemoptysis (within a month), general glandular involvement, meningitis, heart disease, nephritis, epilepsy, etc. Exceptions may under certain conditions be made in regard to nephritis and general glandular involvement. Tuberculin should never be used after acute diseases nor for two or three weeks at least after a febrile attack of unknown cause. In some neurasthenic and hysterical patients the insertion of the needle will cause a rise of temperature. A preliminary injection of distilled water should be given, and it is wise to refrain from a discussion before patients of the symptoms that may occur during the reaction.

Reaction.—In a typical tuberculin reaction the patient begins to feel indisposed about eighteen hours after the injection. This rapidly becomes more marked and he is soon willing to go to or remain in bed. Severe headache, general malaise, pain in the back and limbs, a slight tendency to (increase) cough, loss of desire for food, in some cases nausea and vomiting, and in severe reactions profound prostration occur. The temperature often rises to 101°, but may not reach more than 100° or may go to 107° without apparent ill results. Much importance has been attached to an increase of the physical signs in the chest (local or "organ" reaction), but no perceptible change occurs in a large number of early cases (66 per cent.). The absence of these changes is no proof that a reaction has not occurred. When changes occur they are such as are produced by hyperemia in the tuberculous areas, *e. g.*, rough breathing, wavy inspiration, crepitations, and possibly a slightly higher percussion note. Tuberculous glands or joints may show marked local reactions. The same is true of the larynx. A well-marked local reaction,

even in the absence of a general reaction, including fever, is held by some to be conclusive of tuberculosis. The day following an ordinary reaction the temperature is again normal and the slow fall is rarely seen except in charts when the temperature has been taken throughout the night. In some cases, and even when the temperature is not high, the period of elevated temperature extends over two or even more days. Herpes labialis is not uncommon during severe reactions. The swelling, redness, and pain at the site of injection vary greatly, and may be quite severe, but never proceed to suppuration if asepsis has been preserved.

Among other symptoms more or less inconstant are faintness, giddiness, insomnia, somnolence, fatigue, restlessness, stimulation (rare), weakness, and localizing symptoms, *e. g.*, oppression in the chest, increased expectoration, dyspnœa, and pleurisy (rare). Other foci of tuberculous disease may be discovered by localizing symptoms in the glands, bones, joints, bladder, etc. Marked general and localizing symptoms even with slight rise of temperature (1°) following 0.003 cc. or less of tuberculin may be considered as a positive reaction. A rise of 1.5° to 2° is considered by many essential. When large doses (0.008 or 0.010 cc.) are used, the reaction, to be conclusive, must be typical. A reaction to a small dose is more conclusive of an active focus than a reaction to a larger dose. A second reaction to the same small dose, or a reaction following a repeated small dose, is held to be more characteristic. Rise of temperature or other symptoms immediately following the injection, or a rise of temperature, slight on the first or second day, more pronounced on the third, is not to be attributed to tuberculin.

The sputum may be increased in amount and more purulent. In a number of instances, tubercle bacilli have been first found just after or during a reaction.

The urine shows a marked diazo reaction in a number of instances. If vesical or renal tuberculosis be present, blood and pus as well as tubercle bacilli may occur. Transient albuminuria is not frequent.

The changes in the blood are not constant and show no relation to the severity of the reaction, as manifested by the temperature and general condition. The erythrocytes are little affected, but the leukocytes are usually increased. Tubercle bacilli have been stated to occur in the blood following a reaction. Those who have had most experience with tuberculin have failed to note any dissemination of the disease from its use in man or in animals. Many of the unfavorable results may be explained as coincidences. The untoward results following tuberculin may in practically all cases be attributed to faulty doses or unwise selection of patients.

Results and Statistics.—The most important point to be established in regard to the tuberculin reaction is its specificity. Does the reaction occur in diseases other than tuberculosis, does it always occur in tuberculosis, and can other substances produce a typical reaction in the tuberculous? It must be borne in mind at the outset that a tuberculous focus in any part of the body may produce a reaction and in a suspected pulmonary lesion a reaction is not proof conclusive without further evidence, *e. g.*, symptoms of local reaction, of pulmonary tuberculosis. Undoubted

proof exists that all cases of pulmonary tuberculosis do not react to tuberculin. Healed or completely encapsulated foci are said not to react, though many cases of surgical tuberculosis react long after they have been pronounced "cured." In some advanced cases with tubercle bacilli in the sputum the injection of tuberculin has failed to produce a reaction. Further than this little proof has been adduced to show that tuberculosis fails to react to suitable doses of tuberculin. No case of early or incipient pulmonary tuberculosis has yet been shown to fail to react to a dose of 0.01 cc. or less of old tuberculin. The small percentage of instances in cattle of negative findings at postmortem after a positive tuberculin reaction may be readily explained, where no microscopic study is usually made. Madison's case of a positive reaction with negative findings may be thrown out, for the patient had a temperature varying from 100° to 102° before the injection. Warthin's experience, in which tubercles were found on microscopic examination in the liver of patients who presented no other evidences of tuberculosis, may explain two cases of positive reactions in patients who died shortly afterward and no signs of tuberculosis were discovered at autopsy. An apparently healthy individual (without symptoms and physical signs) reacting to tuberculin need not be subjected to treatment for tuberculosis.

Many diseases other than tuberculosis are said to react to tuberculin. It is a strange fact, however, that in spite of the many opponents to tuberculin, so few authenticated necropsies have been adduced to uphold this view. Many cases that have been reported as examples of other diseases reacting to tuberculin prove on investigation to be of little value and in some cases may be used as arguments on the opposite side. So far no case of syphilis, actinomycosis, or chlorosis which reacted to tuberculin has been proved at postmortem to be free from tubercle.

Many modifications of the tuberculin test have been devised. The *cutaneous* test consists in abrading the superficial layers of the skin over an area of one to two millimeters in diameter, until the pink corium is visible and possibly a pin-point of blood is seen, and then applying a drop of tuberculin and allowing it to remain in contact with the abrasion under a vaccine shield until dry or wiping it off at the end of three minutes. Full strength O. T. may be used but a 25 per cent. solution is usually sufficient. The abrasion should be examined at the end of twenty-four and forty-eight hours and if negative at the end of seventy-two hours. A positive reaction consists in the appearance of a papule and erythema, at least 4 mm. in diameter. This test is positive when tuberculous infection as well as clinical tuberculosis is present, but after the age of seven is of lessened diagnostic value.

The intradermic test consists of injecting tuberculin (usually not more than 0.00002 O. T.) into the skin. This is theoretically far more accurate, as the element of absorption is eliminated. Nearly every patient with tuberculosis reacts to this test. The erythema and induration may be much more extensive than in the cutaneous test.

Tuberculin in ointment (50 per cent.) has been rubbed into the skin (the production of small papules constitutes a reaction) or applied locally to the mucous membrane of various parts, only one of which

we need consider. Tuberculin applied to the conjunctiva produces in sensitive individuals a reddening of various degrees, at times so severe that ulceration occurs in the cornea. The consensus of opinion is that it is wise to avoid this method.

By making a series of simultaneous cutaneous tests, using 1 per cent., 4 per cent., 16 per cent., and 64 per cent., solutions of O. T. and observing the size and difference between the resulting papules, some hold that the activity of the tuberculous process can be estimated.[1]

The opsonic index, complement deviation, and agglutination are of slight aid in diagnosis.

Röntgen Rays.—Lessened excursion of the diaphragm on the affected side, attributed to loss of contractility of the lung, diaphragmatic pleurisy, pressure on the vagus at the affected apex, or to some as yet unknown cause, often occurs early and requires little experience to measure accurately. It is best noted just outside the nipple line. Percussion gives fairly accurate results. The heart is said to be drawn slightly toward the affected side, particularly during deep inspiration, and may be more vertically placed. Deep-seated foci may escape detection by physical examination and be easily detected by the fluoroscope. Considerable experience is necessary to detect slight changes in density, but a diagnosis can be made in patients without physical signs and without sputum. Some stress has been laid upon differences in illumination at the end of deep inspiration. A radiograph taken by an expert may be of great assistance and reveal the presence of a lesion hitherto unsuspected or disclose an area of involvement far wider than the physical signs indicate. In acute miliary tuberculosis it shows some abnormalities of the lungs. Williams records two patients with pulmonary tuberculosis and a negative *x*-ray examination. Stereoscopic plates may show lesions overlooked on the ordinary plates.

Diagnosis of Special Forms.—To separate these forms most reliance must be placed upon the history and symptoms, which alone in nearly every instance will determine whether the disease is acute, subacute, chronic or arrested, by the presence or absence, more or less continuous, of fever, night-sweats, emaciation, weakness, hemoptysis, dyspnœa, cough, and expectoration. The physical signs reveal the damage that has been done, the symptoms whether it is progressing. In a few cases, however, the disease advances so slowly and with so few pronounced symptoms that only careful examinations repeated at long intervals will reveal its slow advance.

Acute Form.—The high temperature, either continuous, remittent, or hectic, the rapid pulse, the hurried respirations with possibly an increase of cough and expectoration, and in some instances considerable cyanosis, all indicate an acute exacerbation. In a certain number of cases in this group the physical signs remain unchanged for some days.

Latent Form.—The physical signs may be very indefinite and the symptoms only those of slightly failing health. In other cases the symptoms only are latent and on examination extensive physical signs are found.

[1] See Morland, *Lancet*, 1912, ii, 688.

Early Form.—In a considerable number of these cases the sputum contains tubercle bacilli, and while the symptoms may be pronounced the physical signs are often very indefinite. The diagnosis depends in many cases, when the sputum is negative, upon the typical symptoms, the absence of any other causative factor, and the tuberculin test.

Advanced Form.—The marked physical signs, usually most advanced at the apex, and the typical symptoms render the diagnosis easy in most instances, but in some types of chronic fibroid phthisis where the expectoration is abundant the tubercle bacilli may be very difficult to discover, and only at postmortem can it be definitely separated from chronic pneumonia. Most of the general and local symptoms are present, and in many instances tuberculous complications in other organs aid in the diagnosis. The presence of the tubercle bacilli is the best criterion.

Differential Diagnosis.—Pulmonary tuberculosis is protean in its early manifestations. Many and various diseases have been mistaken for it, and, what is in many instances more important for the patient, pulmonary tuberculosis has been mistaken for some other disease. We can accordingly divide the following diseases into two groups: first, those which pulmonary tuberculosis may simulate, and second, those which simulate it.

Under the first group belong malaria, typhoid fever, nervous dyspepsia, chlorosis, neurasthenia, and many pulmonary affections, such as simple bronchitis, influenza, idiopathic pleurisy, asthma, and acute and chronic pneumonia.

In the second group are latent suppuration, including endocarditis and pyorrhœa alveolaris, pernicious anemia, exophthalmic goitre, and a number of pulmonary diseases, including influenza, bronchiectasis, pleurisy with effusion, gangrene, abscess, parasitic diseases, actinomycosis, tumor, and pulmonary infarct. The following differential points are of importance. A suspected case without the plasmodium in the blood, with irregular chills and fever and which resists quinine, is usually not malaria. Bronchitis rarely complicates malaria. Acute pulmonary tuberculosis may closely resemble typhoid fever. The onset is very similar, and an initial bronchitis may occur in both. The temperature curves may show a continuous high fever, but oscillations are more apt to occur in tuberculosis. An important point is the cyanosis, which is more frequent in acute tuberculosis. The Widal test, if the patient has not had typhoid recently, may aid. The diazo reaction may occur in both.

Nervous dyspepsia is usually afebrile, and complete anorexia is not usually present. Nervous dyspepsia, especially if occurring with a "stomach" cough, demands an investigation of the lungs and sputum. Many patients with chlorosis are really cases of early pulmonary tuberculosis. Neurasthenia in a mild form should always recall the insidious onset of pulmonary tuberculosis.

Persistent simple bronchitis is rare before the age of forty. Bronchitis occurs more frequently in winter, and fever is of short duration, dulness on percussion is absent, and the rales are diffuse. However, a patient convalescing from a sharp attack of bronchitis may present rales in one

apex for a short time. Emphysema, common in chronic bronchitis, is rare in pulmonary tuberculosis unless the lesion is advanced.

Bronchitis with physical signs limited to one side may be due to influenza, but this should be diagnosed in the absence of tubercle bacilli only when the influenza bacillus is found.

Bronchopneumonia in an adult should be considered as possibly tuberculous even when sputum is absent. A tuberculous bronchopneumonia in children shows higher and more irregular pyrexia, more rapid and profound emaciation, and more sweating. Bronchopneumonia due to streptococci may show night-sweats, loss of weight, cough, intermittent fever, dulness and rales in the upper lobe. The diagnosis in these cases rests solely upon the sputum examination. Chronic pneumonia, rather rare in occurrence, can be diagnosed only by exclusion and after many negative sputum examinations. It is rare in tuberculosis to find advanced disease limited to one side. In simple chronic pneumonia the lesion is most pronounced at the base, in tuberculosis at the apex. The discovery of influenza bacilli or streptococci in a sputum repeatedly negative for tubercle bacilli bespeaks a chronic pneumonia. The number of cases of idiopathic pleurisy is reduced each year as more exact methods for the detection of tuberculosis are introduced. Pulmonary tuberculosis may attack an asthmatic, and asthma may set in early in pulmonary tuberculosis. It not infrequently follows an arrest of the tuberculous disease. The absence of tubercle bacilli and of localized changes, and the *x*-rays separate the two diseases.

Latent suppuration in the abdomen or elsewhere may produce enfeebled breathing in the lungs, and many of the general symptoms of pulmonary tuberculosis. A leukocytosis should arouse suspicion and a careful examination may reveal a suppurating focus in the appendix, tube, gall-bladder, or elsewhere. Localized empyema is usually basic and sputum is generally absent. Subacute endocarditis has been treated for months as pulmonary tuberculosis. The absence of changes in the lungs, the cardiac lesion, and the leukocytosis settle the diagnosis.

Hodgkin's disease with slight glandular involvement, high fever, prostration, and emaciation may closely simulate acute miliary tuberculosis of the lungs. A definite diagnosis can be made only after carefully observing the case for some time, and in many instances is reached only at necropsy. Latent exophthalmic goitre, with tachycardia, very slight exophthalmos, some fever, pronounced weakness, and a marked cardio-respiratory murmur offers considerable difficulty. Resort at times must be had to tuberculin.

Syphilis of the lung may closely resemble tuberculosis, and the diagnosis rests in many cases upon the history, other luetic lesions if present, the results of antiluetic treatment, the Wassermann reaction, and the absence of tubercle bacilli. The root of the lung is found more often involved, while the apex escapes. Destructive or diffuse sclerotic changes may occur in syphilis. Cases occur with fever and slight or indefinite pulmonary symptoms.

Bronchiectasis may so closely simulate tuberculosis that repeated sputum examinations may be necessary to decide the question. Dulness

is more apt to be lacking in bronchiectasis, and the base and posterior are more often affected. When bronchiectasis occurs at the apex the diagnosis is difficult. The history may be important. Early hemoptysis favors tuberculosis, while copious expectoration in paroxysms, which is at times fetid, and without tubercle bacilli or elastic fibers, bespeaks bronchiectasis. It is not uncommon to have bronchiectasis in old tuberculous lesions. In pulmonary gangrene the large quantity of sputum coughed up at one time, its foul odor, its separation into layers, and the absence of tubercle bacilli, as well as the location of the lesion, usually basal, determine the diagnosis.

Some cases of pleurisy with effusion so closely simulate pulmonary tuberculosis that experts have been deceived. The whole of one side may be affected and shrunken. Dulness is more or less marked, resistance increased, and auscultation reveals a distant respiratory murmur, possibly bronchial in character, with pleuritic friction sounds or numerous moderately coarse mucous rales widely heard over the side. The symptoms may be indistinguishable from those of phthisis. Tubercle bacilli are absent from the sputum, and the aspirating needle reveals a thick fluid, perchance with many cholesterin crystals, or possibly a little pus if infection has taken place. Signs of cavity may be present.

The parasitic diseases of the lung most often confused with pulmonary tuberculosis are those caused by the lung fluke (*Distomum pulmonare*) and hydatids. The former disease is quite frequent in parts of Japan and is consistent with years of active life. The most important symptom of this disease is hemoptysis. The discovery of the eggs in the sputum or blood will confirm the diagnosis. In hydatid disease of the lung the presence of the wall membrane or of hooklets in the sputum is pathognomonic. The distribution of dulness may be unusual and excite suspicion. The respiratory murmur and vocal fremitus may be absent. The upper lobe is usually involved.

Actinomycosis is at times readily diagnosed from the sputum. It frequently attacks the chest wall. In anthrax the bacilli are found.

Streptothrix pseudotuberculosa (Flexner), *Cladothrix asteroids* (Eppinger), protozoan infection (Rixford and Gilchrist), and *Aspergillus fumigatus* (Renon) can all produce the same symptoms and physical signs as pulmonary tuberculosis. A careful examination of the sputum in some cases aids greatly in diagnosis.

Tumor of the lung more often simulates pleurisy with effusion than pulmonary tuberculosis, but at times it closely resembles a massive tuberculous consolidation. The abnormal position of the heart and the usual absence of fever are important points in separating it from tuberculous disease. Dyspnœa, fever, and emaciation may be combined in cancer, but it is of rare occurrence. Involvement of the glands may be of late occurrence in malignant growths. The sputum may resemble raspberry or currant jelly.

Slight valvular insufficiency in chronic heart diseases may produce bloody sputum and, if infarct occurs, some temporary fever, pain in the side (pleurisy), rales, and possibly bronchial breathing. In some cases mitral stenosis has been regarded as pulmonary tuberculosis.

PROGNOSIS

The Basis for Scientific Prognosis.—Prognosis in the final analysis depends upon the number and the virulence of the infecting bacilli and upon the resistance of the patient, two factors about which our knowledge is most indefinite in any individual case. Furthermore, their influence cannot be separated one from another. The number of the infecting organisms can never be determined, but the virulence may be roughly estimated by animal inoculation. The resistance of the patient may be indicated by a limited lesion (resistance to the bacillus) or by slight symptoms (resistance to the poison) even when the symptoms (fever, tachycardia, emaciation, etc.) are severe, or the signs very extensive. A double resistance is of course most favorable, and a resistance to poison is, on the whole, more favorable than a resistance to the bacillus, or it may be the latter is more easily acquired or more generally possessed than the former. There is a well-marked tendency to recovery in pulmonary tuberculosis, as postmortem statistics show. In a few patients in an advanced stage the disease shows a self-limitation and intrinsic tendency to recovery. Prognosis can be discussed in regard (1) to the danger to life, (2) to the curability, and (3) to the course and duration. The marked tendency to *relapse* so often present is unfavorable, although relapse after some years of good health, during which the patient has led an ordinary life, is only slightly less favorable than a primary attack. Relapse under favorable conditions is always more serious than under adverse, either in regard to work, hygienic or climatic conditions.

A limited experience often leads one to risk a positive prognosis, but with further knowledge and the recollection of numerous mistakes comes the humility of uncertainty. It is better in all cases to defer a prognosis until the patient has been observed for at least a month or until it can be seen how he responds to treatment. Gee has well said that he who would foretell when a consumptive will die can be sure of but one thing, that he will be mistaken. "In a disease where the unexpected so often happens, where the casual and unforeseen play so large a part, where the patient's wisdom, courage, and self-control count for so much, the prognosis should always be guarded, and a dogmatic attitude avoided" (Lindsay).

Age.—After the fourth semidecade of life, the prognosis with each year becomes less favorable, and after the forty-fifth year it is not good for recovery, but the disease can usually be arrested or, if progressive, runs a slow course. Before the tenth or twelfth year lack of self-restraint would seem to, but does not, render the ultimate prognosis unfavorable. Acute tuberculosis is more frequent in younger patients, but the prognosis in the chronic types is, *cæteris paribus*, at least as favorable as in later years.

Sex.—This, *per se*, seems to exert little influence. Just as the closer confinement to which women are subjected renders them more susceptible, so the ties and household duties which can be less easily avoided than the occupations of the males have a more serious effect. Marriage

complicates the prognosis much more in women than in men, but under certain conditions may aggravate the prognosis in either sex. Puberty and the menopause are considered by some to have an unfavorable influence. Widowhood is serious for both sexes. The rough, exposed life at times incident in the treatment of pulmonary tuberculosis is more suitable to males. However, pregnancy may be considered the most important factor in regard to sex. Women with marked menstrual disturbances are less likely to do well.

Heredity. — The individual susceptibility is held by many to be inherited. It is believed to come from forbears weakened from any form of disease, not necessarily tuberculosis. In general, heredity seems to play a far less important part in prognosis than was formerly thought, and the general opinion today is that, once infected, heredity has little further bearing. Some believe that children of tuberculous parents and grandparents have increased resistance to tuberculosis.

Environment.—The present and future environment of any patient is far more important than the former surroundings. The latter, however, are not without influence, though this may be in part due to the bearing the former has upon the present or future occupation. Patients (males) with outdoor occupations do less well during sanatorium residence than those who have worked indoors. Patients from the country do not do as well as those from the city. The explanation no doubt lies in the greater change. Pulmonary tuberculosis contracted under bad environment is much more likely to do well, when the surroundings are changed than when the disease occurs with good surroundings. Further, the working classes, especially those who do manual labor, are likely to do much better if a "cure" has been effected at home, for in this case a suitable future environment is assured, which is not the case when the patient returns from a sojourn in a health resort to poor hygienic conditions and hard manual labor in order to support a large family.

Patients who find light, agreeable employment without too much responsibility in suitable climates or in the country will do better. Those who return to a nagging wife or family ignorant of the proper treatment should receive a doubtful prognosis. The more nearly the future environment can approximate that under which the "cure" has been effected, the better the prognosis. Patients with ample means should, therefore, receive a better prognosis, but only if they fully realize that money is but an adjuvant, not a true means, to recovery. For all these reasons environment is probably the most essential factor in prognosis after arrest is once established.

Character and Disposition.—The habits are of great importance, and a methodical individual, not too lethargic, has always a more favorable prognosis. A former immoral, dissolute life indicates usually a harder struggle, but the prognosis is worse in those patients who have always followed only their own bent, irrespective of the wishes of others.

A bright, cheerful disposition betokens a better prognosis than a moody, morose, and taciturn temperament. Vacillation, lack of self-control, stubbornness, and lack of imagination or foresight are all unfavorable. The degree of intelligence is important. "I am impressed,"

writes Flint, "with the force of this statement, namely, most patients who recover from phthisis are persons of resolution and perseverence; persons who appreciate the nature of the disease and are determined to overcome it. The disease, as is well known, is apt to induce either delusions concerning danger or a state of passive acquiescence therein. The will may become here, as in some other diseases, an efficient agent in promoting recovery, and it is therefore an important element in prognosis. So far as the mind is concerned, the most favorable condition is that in which the patient appreciates fully the situation and is resolved to spare no efforts in becoming master of it, having much faith in his ability to succeed." Patients who have never been ill or who have always recovered rapidly from illnesses deserve more favorable prognosis. A previous susceptibility to catarrh and colds is unfavorable.

Mode of Onset.—A sudden onset is usually more favorable in that the patient consults the physician at once and does not wait until the disease is far advanced and symptoms pronounced. Patients with an insidious onset or even the catarrhal form may for the same reason present a more serious picture, although in itself the onset affords little aid in prognosis. The pneumonic, gastric, or laryngeal onsets offer usually a worse prognosis. A glandular onset generally betokens a chronic but often a fatal course. An acute onset with extensive or marked physical signs is unfavorable, but the onset may be acute and the patient rapidly recover. An onset consecutive to some debilitating disease, *e. g.*, typhoid fever or measles, is often unfavorable. The mode of onset is connected with prognosis, chiefly in its bearing upon the diagnosis.

Weight.—Loss of weight at first is almost universal and if this approximates one-quarter of the body weight it is of grave import; if it reaches one-third, a fatal outcome is almost certain. A gain in weight under forced feeding is of less hopeful significance than a gain on an ordinary diet, but a rapid gain of some pounds is of vastly less moment than a steady but even smaller gain extending over a long period. A steady loss of weight is more unfavorable than continuous pyrexia, and if both continue when the patient is put under the proper treatment the outlook is particularly dark. In a few cases patients, often chlorotic, go steadily down hill, but lose little or no weight.

The digestion is the keystone in the prognostic arch. If it fails, the outlook is indeed gloomy. As long as it remains good and the patient can take sufficient nourishment there is hope. Patients who always have had a poor appetite, who have eaten little, usually have an unfavorable course (Brehmer). Patients with gastric ulcer often do remarkably well. Marked cachexia is always grave and usually indicates severe chronic tuberculous intoxication.

Fever.—Elevation of temperature is one of the most accurate indications of activity in the pulmonary lesion and for this reason is of vast importance. A temperature curve whose minimum never falls to normal indicates progressive disease better than any other signs. Continuous high pyrexia with marked remissions (as low as 93° to 97°) is usually indicative of septic absorption, cavity formation, and far-advanced disease, with little hope for permanent improvement. Subnormal oral

temperature, if the circulation be good, is of no prognostic significance (especially in winter). Marked fever with slight physical signs, if of any duration, is always of serious moment. The inverse type of temperature curve is a most unfavorable sign. Persistent fever under suitable treatment is far more unfavorable than recurrent fever which quickly responds to treatment, but frequent attacks of pyrexia cloud the prognosis. As long as the nutrition is good there is hope of the fever subsiding. The prognosis is also governed by the time the fever has lasted, and even slight fever (99.6° to 100°) when persistent is ominous. The height of the fever is not of itself a bad sign. Collapse temperatures usually indicate approaching death. Absence of fever may mean immunity to the poison or lack of resistance.

Circulation.—The pulse in the majority is the best prognostic sign, and together with the temperature and weight might be termed the prognostic triad. It is the most sensitive of the three, and the most easily affected by external conditions. A continuously fast pulse, when noted not only in the office but at home, indicates a poor prognosis. A slow pulse with an elevated temperature indicates fever of recent origin or a favorable prognosis. A pulse constantly above 100 during rest is always serious, but a few patients, fully recovered, suffer for years from tachycardia. A pulse out of proportion to the fever indicates that the disease will advance in spite of the low temperature (Sirot). A pulse constantly above 110 indicates a fatal ending. Advanced cases with a normal pulse he found do better than incipient cases with a rapid pulse. Undue irritation of the pulse (heart) is unfavorable.

Cyanosis of the lips, face, and extremities usually occurs only in desperate cases, but many patients with slight cyanosis, especially of the nails, may live for years and enjoy a fairly active life. Cyanosis following hemoptysis, especially if accompanied with tachycardia and dyspnœa, is of most serious moment and death usually occurs shortly.

The arterial tension has not been shown to have any great significance in prognosis. Arteriosclerosis is unfavorable. In pulmonary tuberculosis associated with heart disease, the prognosis is that of the more pronounced disease. Patients with mitral disease do better than those with aortic disease. If compensation be good and the pulmonary tuberculosis slight, prognosis for life is good. Acquired dextrocardia is indicative of chronicity and is not in itself unfavorable.

Hemoptysis.—This may occur as an accident or as a symptom of an advancing process. The prognosis is very different, and when unaccompanied by fever, rapid pulse, shortness of breath, or cyanosis, hemoptysis is often of little moment. The so-called "hemorrhage cases," which are supposed by many to do better than others, have a slightly less favorable prognosis. Hemoptysis is rare in acute cases. In advanced stages with cavity formation hemoptysis is always serious, but an absolutely hopeless prognosis should never be given.

Nervous Symptoms.—In prognosis the nervous system is second in importance only to the digestive and circulatory systems. In all patients in whom the nervous, neurasthenic, vasomotor, trophoneurotic or nervous dyspeptic symptoms are pronounced the prognosis is bad. In

the mentally deficient, or even in those of a low grade of intelligence, the outlook is more serious.

Amenorrhœa.—Amenorrhœa indicates in most cases advanced disease, and is, therefore, of serious import when continued over long periods. Return of menstruation is favorable, but little conclusion can be drawn from a continuance of this function, as it may persist to the end.

Urine.—*Albuminuria* from any cause, if more than transient, is of serious moment. Tuberculous nephritis, if confined to one kidney, may be recovered from, but greatly increases the danger.

Diazo Reaction.—If the patient has no kidney affection, has taken no salol or other drug which affects it, the constant occurrence of the diazo reaction may be considered as an unfavorable sign. The intensity of the reaction is of considerable importance. It is usually connected with fever, and occurs in some cases during the tuberculin reaction.

Blood.—This affords singularly little basis for prognosis. Increase of hemoglobin and of erythrocytes is usually favorable. In advanced cases a decrease of the leukocytes is unfavorable; an increase of the lymphocytes and transitional cells is possibly favorable. Arneth's work upon the polynuclear leukocytes is of limited value. An increase of cells with fewer nuclei is held to be unfavorable, an increase of those with many nuclei of favorable import. The eosinophiles are of little value in prognosis.

The general constitution of the patient is of less importance than would be supposed. Acute types often occur in robust individuals; great muscular strength in a patient with pulmonary tuberculosis demands a careful prognosis on account of the tendency to overexert. On the whole, a good constitution demands a more favorable prognosis than the opposite, although some large, well-nourished individuals give the impression of being "soft" and lacking resistance, while other wiry, thin, flat chested individuals do remarkably well.

The *habitus phthisicus* of itself is not always an unfavorable sign, but fewer patients with such bodily conformity make a good recovery. A paralytic or deformed thorax which limits respiratory movement is unfavorable.

Physical Signs.—Physical signs tell what injury has occurred in the lungs, the constitutional symptoms what is occurring at present, and only by a careful consideration of both symptoms and signs can we hope to arrive at an approximately correct prognosis. Physical signs yield little evidence in regard to activity or arrest in the pulmonary process. The signs of softening for instance are notoriously uncertain. For these reasons physical signs are for prognosis of far less importance than symptoms. The physical signs indicate not the amount of poisoning, but the amount of local reaction of the tissues.

The *site* of the lesion is not unimportant. Unquestionably the disease is discovered earlier at the apex, and for this reason, if for no other, the prognosis is usually more favorable. Primary infections of the base may be due to an overwhelming dose of the infectious material and so are of grave significance. A lesion beginning in the middle lobe is always bad. There is no difference in gravity between the right and left side.

Physical signs, unless consolidation be present, tell unfortunately little of the extent of the lesion in the third dimension (depth). A large portion of the interior of the lung cannot be examined except by *x*-rays, which in many instances yield information most important for prognosis. *Cæteris paribus*, the prognosis, more especially in regard to recovery, depends directly upon the extent of the lesion. As long as the disease is confined to one side the prognosis is better, but slight involvement of both apices is frequent in most favorable cases. Physical signs at an apex and base posteriorly may be produced by tuberculous and non-tuberculous disease respectively, and such cases are more favorable than those with even slighter physical signs which extend from apex to base, and are produced by tuberculosis. In a number of patients moderately coarse rales, rather superficial, can be detected after coughing over the whole of one or possibly both sides. These may be the only physical signs and the patient may be without symptoms. The prognosis in such cases is favorable for arrest as long as great care is exercised. Widely extended pleurisy runs a favorable course (Osler). Scattered foci, even though scarcely perceptible, are always of bad omen, but it is never safe to give an absolutely bad prognosis on physical signs alone. A limited lesion with disease of some duration is always favorable, while an extensive lesion of short duration demands a bad prognosis. Whenever severe symptoms occur with slight physical signs, the prognosis is grave. The mere fact that no definite line of march can be made out is often in itself of the greatest importance, as it may indicate that the disease will run a rapid course (Fowler).

A sharply defined cavity at one apex is more favorable for duration of life than an infiltration scattered over one to two lobes, but the majority of patients with arrest show only signs of infiltration. Excessive fibrosis in both lungs is unfavorable. Leathery, creaking sounds replacing the mucous rales are often the first indication of subsidence of the acute process. Slight changes in percussion and breathing without rales are the most favorable physical signs. The finer the rales the better the prognosis. A complete and constant absence of all rales after coughing is very favorable.

The condition of the unaffected or less affected side must always be carefully determined. Unilateral disease, with shrinking, is always more favorable if accompanied by compensatory hypertrophy of the opposite lung.

A point of special interest is the fact that a patient will often become afebrile, have a lower or normal pulse, less cough and expectoration, gain weight, and in every way indicate that he is improving, and still on examination the physical signs be found more pronounced or scattered over a wider area. The most probable explanation of this fact is that the disease was present in the whole area at the first examination, but the organism was not able to react to its stimulus. As the patient gained strength, the tissues "reacted" and the physical signs increased while the patient improved. The intensity of the lesion is less important than the extent. A sharp demarcation betokens a favorable course.

Sputum.—A gradual change from a purulent to a mucoid sputum is favorable. A sudden change from a purulent to a frothy, watery sputum is of bad omen and often indicates the onset of miliary or acute tuberculosis. When mucoid sputum becomes mucopurulent or purulent an acute process should be suspected, and if it contain elastic fibers and numerous tubercle bacilli where before there were few or none, a more or less extensive softening is present, and if coupled with other symptoms, a doubtful or bad prognosis should be given.

A gradual decrease in the amount of sputum is favorable; a sudden decrease may indicate heart failure, a congestive process, or possibly acute miliary tuberculosis. The absence of sputum is not necessarily a favorable sign. Large amounts of sputum daily for any length of time usually indicate extensive bronchial irritation and are unfavorable. A bronchorrhœa, however, may persist for months and the patient do well.

Tubercle Bacilli.—The occurrence of tubercle bacilli in the sputum always indicates ulceration and such patients have accordingly a less favorable prognosis. The longer tubercle bacilli occur in the sputum the less favorable usually the prognosis.

The unequal distribution and the possible variation in staining of the bacilli, the temporary occlusion of the focus, the fact that patients with rapidly advancing disease may give off few bacilli and fully encapsulated cavities in arrested patients, enormous masses, visible when stained to the naked eye, all emphasize great caution in prognosis from the number of bacilli. An early disappearance and persistent absence of tubercle bacilli during treatment is most favorable.

Morphology affords little aid, but short bacilli are usually held to indicate an active growth of the infecting organism, and so an unfavorable prognosis. Long, slender, beaded, irregular bacilli indicate a chronic course, but not necessarily a favorable termination. The same is probably true of the bacillary fragments, "splitter."

Secondary infection is *a priori* unfavorable, but owing to the great difficulty in diagnosis cannot be relied upon for prognosis.

Elastic fibers are now seldom found in sanatorium patients and their constant presence is of very unfavorable import. Fibrinous coagula (fibrinous bronchitis) are of bad prognostic omen.

Complications.—The occurrence of any complication is of unfavorable moment, but all of a tuberculous nature bespeak a lessened resistance and are accordingly of grave prognostic significance. Simple acute or even chronic *laryngitis* is of slight importance, but tuberculous laryngitis makes the prognosis at once grave. Slight ulceration of the cords without infiltration is the least unfavorable form. When complicated with dysphagia the condition is most serious. Simple acute *bronchitis*, especially if the attacks are frequent, clouds the prognosis. In advanced stages it may be the primary cause of death.

Dry *pleurisy* as a complication, even if extensive, is not unfavorable. The effect of a pleuritic effusion depends partly upon the size of the effusion, partly upon the stage of the disease. As an onset it is distinctly favorable; during the course it exerts little influence. Hemorrhagic

effusion is always serious. Empyema is rarely recovered from. *Pneumothorax* is always most serious and recovery is of the rarest occurrence.

Non-tuberculous *enteritis* seems to be well borne, especially if of the neurotic type. Tuberculous enteritis occurs usually late in pulmonary tuberculosis, when the fatal termination is not far distant, but recovery can take place.

Arthritis, rheumatic fever, mitral stenosis, cardiac hypertrophy, slight emphysema, bronchial asthma, and gout have all been held to exert a favorable influence on pulmonary tuberculosis. Typhoid fever is not necessarily unfavorable. Diabetes mellitus, pulmonary stenosis, pulmonary gangrene, lardaceous disease, tuberculous stomatitis or pharyngitis, severe thrush, meningitis, œdema, melancholia, insanity are always of very grave if not fatal prognostic significance. Mild diphtheria exerts but little influence when properly treated. Syphilis is said in the early stages to be unfavorable, but is certainly well borne in many patients who ultimately recover. Bronchiectasis is unfavorable. Enlargement of the thyroid is not unfavorable unless accompanied by symptoms. Tuberculous otitis media and slightly enlarged lymph glands occur in patients whose disease runs often a chronic and possibly an unfavorable course. Persistent anemia is unfavorable. Fistula-in-ano exerts little influence and is not unfavorable. Chronic peritonitis, even if pelvic, is unfavorable.

The duration of treatment is important. Little can be expected from a "cure" of less than three months, and the best results are those obtained after three or four years.

Prognosis is always uncertain. The anamnesis is of less value than the actual condition. Symptoms are of more value than physical signs, and are, in the order of their importance, those referable to the digestive tract (including weight), to the nervous system (including character), the pulse-rate, and the fever. Complications, especially if tuberculous, are always to be dreaded. The urine, the sputum, and the blood are of far less value in prognosis than the foregoing. Race, age, sex, heredity, mode of onset, the shape of the chest, spirometry, etc., are of only secondary importance, and, like the urine and sputum, helpful if they concur with the symptoms and physical signs, of little value if they contradict them. The financial condition and the environment of the patient should always be considered.

PROPHYLAXIS

Prophylaxis can be reduced to two fundamental factors—destruction of the specific germ and increase in the individual resistance. The chief source of tubercle bacilli in the air is the sputum, dried and ground into dust or (of less importance) sprayed into the air in coughing. The tubercle bacillus is not ubiquitous, and is usually found only near the tuberculous patient. The individual resistance is probably what has enabled any individual of middle age to escape serious infection. The struggle to raise the resistance begins at birth and continues through

life. The crusade must be against tuberculosis and not against the tuberculous patient.

State and Municipal.—Prophylactic measures can never be as immediately efficient as similar measures against other infectious diseases. The majority of instances of acute infectious diseases are in children; the number of individuals attacked at one time in a community is limited; the date of onset and of full recovery can be closely approximated; the infectious period is short and coincides in part at least with restricted movement due to disability, and the economic loss is slight. In tuberculosis, young adults are attacked chiefly, the onset is frequently overlooked, the number of individuals attacked at one time is much larger, the movement is little restricted for months or years, as the disability is often slight while the infectiousness is great, and the economic loss enormous. So many and varied etiological factors enter into infection in tuberculosis, and so many of these are so closely bound up in the individual relations, that it will never be possible to legislate against tuberculosis as against smallpox or plague. Prophylactic laws should be passed governing the army and navy, the restriction of animal tuberculosis, and the sale of tuberculous milk and meat. The notification of tuberculosis; the regulation of trades, workshops, and traffic; the construction of houses, including tenements; a campaign of education, and the erection of special hospitals, dispensaries, and sanatoriums should be carefully dealt with.

Army.—The question of prophylaxis is one of importance, especially for all countries where military service is compulsory. Individuals formerly tuberculous should be exempt from military service and all recruits with a suspicious history should receive a careful and thorough examination. Repeated examinations of the chest and sputum should be made. Barracks should be properly constructed, periodically disinfected, and all rules of individual hygiene, especially those about promiscuous expectoration, strictly enforced. The army should have its own sanatorium, where patients should be sent at once.

Navy.—The confined quarters, almost of necessity overcrowded and ill-ventilated, even of the battleships today, render the men more susceptible. The greatest care should be exercised in the preliminary examinations, especially before long cruises, and about sputum disposal. The smaller craft, plying along the coast, should be carefully inspected and placarded, and notification of pulmonary tuberculosis should be insisted upon, in order to carry out disinfection.

Regulations against Animal Tuberculosis.—Convincing proof has been adduced that the human and bovine diseases are intercommunicable; and even if infection with the bovine tubercle bacillus occurs less frequently, it should, nevertheless, be vigorously combated.

Dairies.—Model dairies have been started in many States and countries, and Coit, of New Jersey, has patented the term "certified" to insure that all dairies using it dispense milk approved in regard to purity and quality by a medical committee of the community. All cows must be tested with tuberculin before admission to such byres, and after admission retested at intervals.

Milk from tuberculous cows with healthy udders has been found infectious. Such milk has been considered safe after boiling, but Smith has pointed out that boiling even for ten minutes is sufficient only if no pellicle forms upon the surface, and Calmette and Breton have recently asserted that dead tubercle bacilli in such milk are injurious and affect healthy guinea-pigs like small, repeated doses of tuberculin. All milk from an uninspected dairy should be boiled or heated in this way especially if used by children, invalids, or convalescents. Properly boiled in a double kettle (boiler), with a rather close-fitting cover and cooled at once without uncovering, the taste is said to be unchanged.

Tuberculous cows should always be isolated, not housed; and it is wiser to use them only for breeding or working purposes, removing the calves at birth, as only one-third of 1 per cent. are tuberculous at birth (Bang). Cows with tuberculous mastitis, metritis, or enteritis should be killed. Cattle once reacting to tuberculin should be branded. Repeated injections may produce a tolerance, a fact made use of by unscrupulous dealers. Cattle which have been on a journey generally react but slightly for some time, due probably to the inhibiting effect of mental excitement on the heat centre (Bang).

The method of vaccination with living bacilli produces immunity for a limited period only. Immunized calves should be fed on milk from cows free from tuberculosis.

Slaughter-houses.—Tuberculous meat is of far less importance than tuberculous milk. The danger of such meat lies in the fact that the centre of a "roast" is not sufficiently heated in cooking to kill tubercle bacilli (Woodhead). Cattle from the Western plains, and, in fact, all cattle, excluding milch cows, are rarely tuberculous. About 40 per cent. of milch cows are said to be tuberculous, however, and as these are usually slaughtered for "home" consumption, they are rarely, at least in America, properly inspected. For this reason public slaughter-houses where inspection can properly be carried out are of great value.

Tuberculous fowls should be destroyed. Generalization of tuberculosis is much more rapid in the hog, which is frequently tuberculous, and greater care should be exercised in the use of its flesh.[1]

The danger from bread, from uncooked fruits and vegetables, unless handled by tuberculous patients, is so slight that it may be neglected.

Education.—Probably the most important and farthest-reaching prophylactic measure is education of the people in matters pertaining to hygiene. In the kindergartens and primary schools short lessons in general hygiene and the danger of spitting upon the floors should be given. In more advanced schools the lessons may deal with the prophylaxis of pulmonary tuberculosis. The danger of coughing without covering the mouth should be made clear. Children as well as adults should have the reasons for rules explained to them. It has been suggested, and even put in force in some countries, that a summary of the important elementary principles of hygiene be printed upon covers of

[1] See H. Sessions, Cattle Tuberculosis, for an excellent *resumé* of the whole subject of animal tuberculosis.

school-books. Excellent rules for school-children have been formulated. Goodall has written a most useful pamphlet for teachers.

Education, however, should not stop in the schools; it should be carried to the adults by means of popular illustrated lectures, at halls convenient to the classes it is intended to reach. Every city should have its permanent tuberculosis exhibit or museum, where at frequent intervals demonstrations should be held.

Especial attention must be given to the education of those constantly exposed. It is not sufficient to give the tuberculous patient a few general rules, particularly if he is not very intelligent. Written or printed rules in detail should be left with the attendants, but they should be fully explained orally. In some cases it is wise to tack up a card where it can be seen by all the household and serve as a constant reminder.

Notification.—This has been widely adopted. Good results have been obtained by voluntary notification, stimulated by a small fee for each case. The chief objection is the publicity which is supposed to be attached. Laws should be passed making it a serious misdemeanor for the health officer to allow any but a duly authorized official to have access to the records. The public should be informed that notification does not mean placarding the house nor placing any restriction upon personal liberty as long as a reasonable amount of care is maintained.

It should be made compulsory upon the patient, his family, and his physician to report to the sanitary officers a change of residence. Proprietors of houses should not be made responsible for reporting a change of residence, as it would quickly work great hardship upon the patients. The value of notification in relation to inspection and disinfection is difficult to overestimate.

Biggs has found that many physicians who fail to report cases will readily fill out a blank containing the required information when free sputum examinations are made. In New York no action is taken about cases in private houses or where the physician indicates that he is willing to instruct the patient and family.

The House.—"Consumption may well be termed a house disease," writes Flick. "Without the house it would not exist. It depends upon the house for its implantation, propagation, and for evolution of all its phenomena. The house is the place where the tubercle bacillus lies dormant in wait for its new host; it is the place where the new host gets its implantation; it is the place where the tuberculous subject gradually becomes a consumptive; and it is the place where the consumptive dies."

Two important factors in regard to the house have long been known to and insisted upon by sanitary experts, precautions against overcrowding and proper ventilation. A third important factor has only very recently been introduced—disinfection.

Overcrowding.—It has been clearly shown (for London) that the important feature in overcrowding is less the number of inhabitants per acre than the average number per room, and the mortality, further, is lower where each person occupies a single bed. At least 600 cubic feet of air space should be allowed for every adult and at least 400 for

every child (Biggs). The tuberculosis death-rate is directly proportional in France to the size of the city (the larger the city the greater the overcrowding), but Graux thinks overcrowding of less importance in Paris than deficient ventilation and sunshine.

Ventilation.—Direct sunlight kills the tubercle bacillus in thin layers of sputum in five or six hours and diffused sunlight in several days. Proper ventilation greatly facilitates this bactericidal action. The height of the house should not exceed the width of the street. "Back-to-back" houses greatly increase the tuberculosis death-rate. Biggs thinks that houses built in lots 25 x 100 feet should not occupy over 60 per cent. of the surface of the lot. Menusier found the death-rate more or less proportional to the number of stories. Lodging-houses should be provided with an automatic and adequate system of ventilation not under control of the lodgers. Partitions in lodging-houses, built upon the cell plan, should be raised eight inches from the floor.

For dwelling rooms 3000 cubic feet of fresh air per head are needed every hour. Adequate provision should be made for parks in all cities. It has been aptly said that in the country the only bad air is in the farmers' houses, whence it seldom has an opportunity to escape.

Disinfection.—Disinfection of all houses which have been occupied by patients with pulmonary tuberculosis should be made mandatory by law. It should be required each time a patient changes his residence. Sleeping cars, particularly those occupied by patients on their way to health resorts, should be fumigated at the end of each trip. Rooms in hotels occupied by patients should be disinfected on vacation. All disinfection should be performed by the sanitary officials. In open health resorts frequented by patients with pulmonary tuberculosis, each boarding-house or pension should be required to have its rooms numbered, to keep a register of inmates, and to notify the health officers of removal or death of the inmates.

The best means of disinfection for rooms is formaldehyde vapor. At least 8 ounces (250 cc.) of the commercial (40 per cent.) formalin should be used for each 1000 cubic feet of air content. Inasmuch as the efficiency of formalin is directly dependent upon the strength of the vapor it should be vaporized as quickly as possible. The most efficient method is that employed by Biggs, of New York. For an ordinary room (1000 cubic feet) 1 pound (500 gm.) of lime, 8 fluidounces (250 cc.) of formalin, and 2.5 to 3 fluidounces (75 to 90 cc.) of commercial sulphuric acid are required. All openings but the door are sealed. The formalin is poured into an empty water pitcher, 4 ounces of water added, and the sulphuric acid poured slowly in. The lime is placed in a china or earthenware wash-basin on the floor upon newspapers, all water removed from the room, all drawers and cupboards opened, the mattresses stood on end, and the mixture poured quickly upon the lime and the door sealed. The sulphuric acid may be packed in a tin bucket containing the lime, and with the formalin in a separate bottle may be used by any person of ordinary intelligence. The room should remain closed at least six but better for twelve or eighteen hours. Dried masses of sputum should be soaked with a 2 per cent. solution of calcium hypochlorite and

carefully removed. Paraform candles are effective for small spaces, such as closets.

In regard to the other disinfectants, commonly employed, much diversity of opinion exists. Phenol (5 per cent.), corrosive sublimate (0.1 per cent.), copper sulphate, and numerous others have proved in many instances unsatisfactory. It should, however, never be lost sight of that after formalin or any disinfectant thorough cleansing is imperative. A room which has been thoroughly cleansed and carbolized is safer than a room in which formaldehyde has been used and cleaning neglected. Thoroughly wetting the ceilings, walls, floors, and furniture with 1 to 2 per cent. solution of chlorinated lime (1.5 ounces to a gallon), applied with a Turk's-head brush, gives excellent results. Where this cannot be done, rubbing the walls down with bread-crumbs or dough may be of value.

After death or removal the entire place should be renovated. The model requirements in force in New York City include, besides disinfection, scrubbing the painted woodwork with a solution of hot soda, repainting, repapering, or recalcimining the walls. These methods are efficient in ridding an apartment of tuberculous infection which even with efficient disinfection it is hard to accomplish. They are easily understood, improve the premises, consequently are cheerfully acquiesced in by the tenants and almost always promptly carried out by the owners (Biggs).

Clothing.—Hangings, bedding, mattresses, pillows, and rugs should be disinfected with steam. All articles of little value and all old books and papers should be burned. All soiled linen should be boiled. Tubercle bacilli live the shortest time on white enamel paint.

Tenements.—The tenement house is a hot-bed for pulmonary tuberculosis. Model tenements have been erected in many cities and laws governing their construction passed. Buildings, hopelessly bad, should be condemned and pulled down.

Institutional.—In all institutions tuberculous individuals should be separated to some extent. Tuberculous patients should be admitted to a general hospital only if no special hospital exists. They should then occupy separate rooms and should under no condition be allowed to enter the general wards. Hospitals for the insane should have separate pavilions for their tuberculous inmates. Nurses and attendants in such pavilions would often do well to wear masks. Patients with pulmonary tuberculosis should be absolutely prohibited from living in common lodging-houses (Biggs).

Prisons.—Mortality from pulmonary tuberculosis has long been so high in prisons and reformatories that sentence for a term of years is almost equivalent to a sentence of death by consumption (Johnston). The conditions in the county jails are often much worse than in the penitentiaries. Each prisoner should be examined at once and if found tuberculous should not occupy a cell with a healthy person. After death or removal, the cell should be carefully disinfected. Ransome thinks whitewashing of little value and possibily of danger, through scaling and dust. Tuberculous should not be placed near healthy

prisoners in workshops, should have lighter if any work, and the proper disposal of the sputum should be provided for. No tuberculous prisoner should be pardoned until his future environment has been carefully considered.

Schools.—School rooms should be well lighted, ventilated, and sunny. The floors and walls should be so constructed that they can be washed and not swept (dry) or dusted. Hygienic drinking fountains with an upward flow should be placed in every school and the common drinking cup should be abolished. In doubtful cases the books should be disinfected. Slates should not be used. It would be a wise measure to inspect all boarding schools and their staffs at intervals. Tuberculous teachers, scholars, and janitors should be excluded until their sputum has long been free from tubercle bacilli, and unquestionably it is better both for scholars and teachers to exclude them permanently. Special schools, held out-of-doors, should be maintained for all tuberculous children.

Factories and Shops.—"The home and the workshop are the two places where environment of sufficient intensity for contamination and contact of long-enough duration for implantation can most readily exist" (Flick). The minimum air space per individual, proper ventilation and lighting, sufficient floor space, the substitution of mopping or washing for dry sweeping, absolute prohibition of spitting on the floor, a sufficient number of suitable cuspidors, proper medical inspection, limitation of hours, and regulation of hours for meals in a suitable place apart from the workshop, removal of gases, vapors, and dust, should be established in all workshops. Sleeping in workshops should be prohibited. Occupations entailing much exercise require more ventilation and less warmth than sedentary trades. It is advisable to paint all walls for about six feet from the floor with enamel paint.

Trades.—Some trades are especially dangerous and measures should be taken to protect the workmen. Appliances for removing dust in potteries, glass- and stone-cutting, polishing and grinding, hoods for noxious vapors, such arrangements of benches and machinery that the workmen will not have to sit or stand for hours in cramped positions, should all be provided. Certain trades should be scheduled as dangerous and be absolutely prohibited in sleeping rooms. Persons with tubercle bacilli in their sputum should not be allowed to handle or to prepare food for others, nor should they attend non-tuberculous invalids. Dentists should always sterilize all instruments. Coal-mining, lime- and gypsum-working, and tanning have been looked upon as lessening the chances of disease. The trades unions would do well to strive vigorously for these reforms.

Traffic.—"Sleeping-car" infection no doubt occurs, but its importance has been exaggerated, although we should not for this reason relax our efforts for clean cars. Every coach that runs to a health resort should be disinfected with formaldehyde at the end of each trip. The construction should be as plain as possible. The vacuum system of cleaning has been successfully used. Dry sweeping *en route* should be prohibited. Brushing off passengers should be restricted to the rear end of the car

or prohibited altogether. The question of cheap individual drinking cups for travellers is of as much moment as any other problem.

Street railway cars, "electrics," trams, and omnibuses would seem to be a grave source of danger. Flick states, however, that after some investigation he fails to find pulmonary tuberculosis more prevalent among conductors of these cars than among the general population. The majority of such conveyances are wretchedly ventilated and disinfection is rarely if ever carried out except for smallpox.

Hospitals.—Many competent observers hold that the great reduction and the low mortality in England are due to the establishment of hospitals for patients in far-advanced stages. These institutions are by far the most important in the antituberculosis crusade. Infection when happening usually occurs from those in the last stages.

Such hospitals should be founded by every municipality of 100,000 or more inhabitants. They should be situated in the healthy, wooded suburbs, and easy of access. Further provisions for the open-air treatment should be made, for isolation without attempt at cure is deplorable and cruel. The grounds should be inviting and no opportunity spared to make the whole institution as attractive as possible. The average stay in such institutions may be said to be about six months.

When after notification the sanitary inspectors feel that proper precautions cannot be taken by the family in the case of a very ill patient, or that the patient insists upon breaking all prophylactic measures, if necessary he should be removed to the institution. It is safe to say that such a course will have a deterrent effect upon the most refractory patient and that actual forcible removal will seldom be necessary.

Dispensaries.—Next in regard to prophylactic value stand the tuberculosis dispensaries, aptly termed preventoriums. The dispensary physicians should after careful consideration decide what is best for each patient. He should be visited at home and fully instructed in hygienic measures. Other members of the family should be examined. Printed directions for the patient and for prophylactic measures for the family should be fully explained and left for reference.

Sanatoriums.—The value of sanatoriums lies chiefly along two lines, education and arrest of patients in the "closed" stages. While 60 per cent. of the "open cases" still have tubercle bacilli in their sputum on discharge, the education they have received in the sanatorium renders them so careful that in most instances they are of little or no danger. Sea-side sanatoriums for children are most important, but day sanatoriums which receive advanced cases have a great value.

The municipal campaign against pulmonary tuberculosis as outlined by Biggs should, therefore, include: "(1) Compulsory notification; (2) suitable plans for the education of the people, including visitation and instruction of cases, especially in tenements, lodging-houses, boarding-houses, and hotels; (3) a complete and efficient scheme for disinfection and renovation of premises after death or removal; (4) supervision of shops, occupations, and conditions where consumptives are employed; (5) a hospital equipment, consisting of a reception pavilion for patients, suitable institutions within or near the city limits for the care of

advanced, and a country sanatorium in a well-situated locality for incipient cases; (6) power of compulsory removal and retention in hospitals when necessary." The addition of one or more dispensaries for pulmonary tuberculosis, situated in the midst of the poorest and most thickly populated districts of the city, in easy access of the street railways, would make such an organization nearly perfect.

General Prophylaxis.—General prophylaxis dealing with sputum, its collection and destruction, coughing, rules for the tuberculous patient, and the cleaning of the house, strike at the fountain head of infection. If we could cut off the supply of infectious material from patients, infection would soon be reduced to the vanishing point (Woodhead).

Expectoration.—Careless expectoration is the chief source of infection. Laws should be passed in all cities prohibiting spitting upon the pavement, the floors or steps of public buildings, of elevated railway platforms, of waiting rooms, of all cars and steamboats, especially ferries, of wharves, public carriages, places of public entertainment, cafés, restaurants, shops, hotels, prisons, and boarding schools. These laws should be posted in all such places. It is not enough, however, to pass such laws—they must be enforced. No community has worse laws than it deserves and the enforcement of all laws is in the hands of the people. Not until public opinion is aroused and the public educated up to the fact that sputum is as nasty, as loathesome as, and in most cases more dangerous than, other dejecta (urine and feces) can the spirit of anti-spitting laws be carried out. It is useless to try to prevent patients with tuberculosis from expectorating and allow the general public to do so.

Disposal of Sputum.—All signs forbidding spitting should be accompanied by others, indicating where to spit. All persons should be advised to spit only when necessary and then to deposit the sputum, if at all possible, in water. Patients should be told that it is for their own interest not to expectorate except into a proper receptacle. That the only dangerous sputum is dried sputum cannot be too often emphasized.

Spittoons should be provided in all public buildings, places of assembly, cars, and along all stairways. They (1) should be of metal or unbreakable material (to avoid infection by scratching), (2) should, as far as possible, conceal the sputum, (3) must not allow their contents to spatter, must be placed breast high, (4) must be easy to clean and hard to upset. The ordinary slop-jar answers these requirements much better than the spittoons ordinarily employed. Spittoons should contain some antiseptic fluid, preferably one that digests or dissolves the sputum, although plain water will answer. Sand, bran, sawdust, or ashes should never be put into receptacles for sputum. The caustic alkalies in strong solution are very efficient.

Spittoons with constantly running water are excellent for the general public, but should not be used in sanatoriums or hospitals.

Sputum should be carefully guarded from flies, which may widely disseminate the tubercle bacillus.

The advisability of doing away with spittoons in physicians' offices, dispensaries, and sanatoriums should be carefully considered. It is not necessary for physicians, even in health resorts, to have spittoons

in their offices. A few paper cuspidors, under a notice stating that every patient who expectorates should have a pocket cup, are far more cleanly, less disagreeable, just as practicable, and emphasize a most important measure. General sputum boxes or spittoons in sanatoriums lead to carelessness, are often the seat of accidents, and should be abolished. Everyone should be encouraged to use sputum boxes when suffering from pneumonia or other even slight respiratory diseases.

A perfect pocket sputum cup or flask has not yet been devised. Many patterns have been put on the market, but none are much better than Dettweiler's. The essential points of a good pocket cuspidor are that it should be easily managed, preferably with one hand; perfectly tight; not too bulky; easily cleaned, and so constructed that sputum does not adhere to the cover when opened.

The "cup" devised by Major D. W. Appell, U. S. A., consisting of thin, impervious card-board, so folded as to form an envelope which contains a bit of cotton, is very satisfactory for patients who expectorate but little or for use while walking. The main objections to it are the filaments of cotton that float off in the air each time the box is opened, the small capacity, and the tendency to spill unless always carried upright in the pocket. The "sanitary cuspidor," consisting of a metal (tinned-iron) frame, holding a waterproof thick paper cup, so folded that flanges prevent spilling if accidentally overturned, is probably the best for use at home and in sanatoriums. The advantage of both these cups is that they need little handling and can be burned daily. The papers in the metal frames should be changed daily, the cup filled with sawdust and wrapped in paper and placed handy (in a special box) for collection by an orderly, who should wear rubber gloves. The metal frame should be washed in carbolic acid each day.

The use of cloths or Japanese napkins is not to be recommended, but is at times necessary for the very ill or very poor. Each cloth or napkin should be used but once and immediately deposited in a paper bag or a newspaper folded into a bag. This helps to prevent drying, does away with a second handling, and facilitates burning.

If cloths or paper napkins are used, the hands should be frequently washed, for Baldwin has shown that unless the patient is scrupulously clean the hands are frequently soiled. The handkerchief should never be used for sputum nor employed to wipe the lips after expectorating, but a special cloth should be kept for this purpose.

Sputum may be disinfected by heat (burning, boiling, steaming) or by chemicals. The best method is by burning, which may be done in a special crematory or one connected with the general heating system. In the home the kitchen stove and a hot fire are all that is necessary. The boxes should be carefully placed upon the fire. Boiling when used should be continued thirty minutes. Disinfection with live steam is efficient and renders the sputum fluid, but is expensive. Destruction by chemical means is usually expensive and not always efficient.

The emptying of sputum cups into drains or water-closets should never be permitted in hospitals or sanatoriums. Putrefactive organisms have little effect upon the tubercle bacillus, which may live in drain

water for 194 days. Moeller's work has shown the danger of throwing sputum into sewage-disposal plants, especially when the water is afterward used for irrigation. He found tubercle bacilli on radishes.

Coughing.—Patients should always hold a cloth (not the hand) before the mouth on coughing or sneezing. This cloth should be frequently changed and burnt and not used as a handkerchief. The danger from "shaking out," before using a handkerchief or cloth in which tuberculous sputum has been deposited, is probably a more serious menace than the droplets from coughing. Telephone mouth-pieces should be cleansed frequently and the cheap paper disks, to cover them, deserve wide use.

Feces and urine, even when the alimentary and genito-urinary systems are apparently free from tuberculosis, may contain tubercle bacilli. For disinfection, chlorinated lime, carbolic acid, or burning should be employed.

Rules for Patients.—All patients should be instructed about personal cleanliness, and they should be fully alive to their duty to the public, for until this is realized little effective prophylaxis can be accomplished. Beards and moustaches should be worn short, if at all. Kissing should be forbidden. The hands should be frequently washed and the patient cautioned about touching any articles of food intended for others. Carelessness about the sputum should not be tolerated. The patient should have his own bed, four feet distant from another, and, if at all possible, his own room. It is unnecessary, when the patient comes to the table, to have special dishes and silver if care be exercised in washing, but when confined to bed his tray and dishes may be kept apart and washed separately. The patient's room should be carefully cleaned, never swept, and 5 per cent. carbolic acid solution used freely. Disinfection of both room and clothing of the well-to-do patient when any possibility of infection has previously occurred is not without its advantages. The room should be furnished with washable curtains; carpets and draperies should be removed and one or two rugs provided. The blankets should have washable covers. The walls should be painted, preferably with white enamel. The patient should have the sunniest, best-ventilated room in the house.

House.—Dampness is conducive to pulmonary tuberculosis, and the soil and subsoil, therefore, should afford ample drainage. The cellar should be cemented. There should be no inside rooms and all rooms should have two windows. The window area should be at least one-seventh of the floor space. Too many trees should not be permitted close to the house. Dry sweeping should be abolished and all brooms covered with bags which have been moistened in some antiseptic solution. A vacuum cleaner should be used when possible. Both mops and cloths should be boiled or soaked in some disinfectant.

Laundry.—The infection of workers in laundries can be prevented. In all hospitals and sanatoriums the personal and bed linen should be handled as little as possible. It should be placed in bags, and, on reaching the receiving room of the laundry, put in the sterilizer, which should be the only communication between the receiving and assorting rooms. All blankets, pillows, and mattresses should be disinfected with

live steam and formalin. Blankets can then be washed. Especial care should be taken of handerchiefs, which should always be gathered in bags and disinfected. A wire basket, attached by clamp to the head of the bed, has been devised to hold cloth and cup. This prevents soiling of the sheets and bed linen.

Servants.—The danger of infection from tuberculous house servants is not sufficiently appreciated. Their close confinement, small, poorly lighted, and wretchedly ventilated rooms often act like a boomerang.

Domestic Pets.—Fondling or kissing parrots, dogs, cats, or canaries may in rare instances transmit tuberculosis, but the danger is slight.

Churches.—It is a natural instinct, that, as man realizes that human aid is of no avail, he should turn to the church. Bishop Fano, of Italy, realizing this danger, has recently issued a circular to priests, advising the use of sawdust in sweeping, and the washing of the grate of the confessional with lye once a week. The use of individual communion cups, which should be carefully cleansed after use, is growing rapidly and should be encouraged.

Burial.—While some very slight danger may arise from the bodies of tuberculous animals, buried at an insufficient depth, such danger may be neglected in the case of man.

Individual Prophylaxis.—The very nature of the disease, its simulation of catarrhal bronchitis and other benign diseases, will always make individual prophylaxis of much importance. To two classes it is of especial value, to the very young and to the predisposed.

Prophylaxis should begin at birth, especially if the child comes of parents weakened through any disease. If the mother be the subject of tuberculosis she should not nurse the child, both for her sake and the child's. If the child come of tuberculous or weakened forebears, no means must be omitted to strengthen and harden it. The baby should be given over to a healthy nurse and its intercourse with the tuberculous mother should be as limited as possible. In no case should it occupy the same bed. The milk should be "certified" and modified to suit the child's need. If not "certified" it should be heated to 180° to 190° F. The nursery should be the sanctum of every household and visitors should not be allowed to enter it. The children should be brought down to the visitors, and they should be taught not to kiss strangers and to keep everything out of their mouths. It is a wise plan to taboo street shoes and trains from the nursery. It is here that dust should never be found. At first the child may be confined to a clean blanket placed upon the floor, but this is not possible later. He creeps and crawls everywhere in the room. The bacterial flora of the floor is soon to be found on his hands and under his nails. What is on the hands of children is soon in their mouths. Every little draught and every little movement of any kind stirs up the dust, often just high enough for the crawling baby to inhale it. The floor, therefore, should be scrupulously clean and with as few cracks as possible. A heated tile floor with tiled walls makes an ideal nursery. A broom should never enter this room, which should be bright, sunny, and well ventilated. Children should never be allowed in a consumptive's room unless it be for only a moment.

In the third to the fifth year the child should be gradually accustomed to cool and then cold sponges, given while standing in warm water. The house temperature should be 65° to 68° F. and the air not too dry. The nursery should be flushed several times a day with fresh air and a window should be constantly open at the top, day and night. For the predisposed hyperventilation is necessary. It is often well to have a second room, which the children can use for a few hours every day, and it is always preferable that the attendant sleep in an adjoining room. The hours out-of-doors, especially for predisposed children, should be gradually lengthened in winter and nearly as continuous as in summer. The ideal place for such children is the country or an open suburb. If not strong when the school age arrives, all thoughts of indoor study should be abandoned and interest aroused in nature.

Nasal obstruction causing mouth-breathing should receive appropriate treatment. Every effort should be made to keep the mucous membranes healthy. At an early age these children should be taught self-restraint and unselfish habits. The chances of escape or recovery from pulmonary tuberculosis are often lessened by neglect of this rule.

The employment of tuberculous midwives, the practice of ritual circumcision by a tuberculous rabbi, tasting the child's food, chewing it before feeding, or blowing upon it, are all strongly to be condemned.

As the child grows older he should be taught to hold himself properly and outdoor sports of all kinds should be encouraged, but care taken to regulate them to his strength. A well-ventilated gymnasium is excellent for exercise (during the winter months) in bad weather. Special exercises leading to increased development of the chest and lungs are valuable. They should always be taken in the open air or before an open window.

Plain, simple, nutritious food is of great value. Milk and easily digested fats, such as cod-liver oil, should be freely used. Especial care must be taken of bad eaters, for these are very susceptible (Brehmer).

Change of climate, a sojourn at the seashore or in the mountains, is of great assistance to many youths and girls, especially about the age of puberty. Long sea voyages and ranching are also good. These are especially valuable just about the age at which other members of the family have developed the disease. Doenitz has proposed tuberculin treatment for all predisposed individuals. Any individual who is ten pounds or more under weight should take precautionary measures in regard to pulmonary tuberculosis.

Choice of a Profession.—The choice of a profession for predisposed individuals is a difficult task. They should if possible choose an outdoor occupation which does not entail too much exposure to inclement weather. A change from an outdoor to an indoor calling often results disastrously, and Burgeois has called attention to the danger of the city for rural inhabitants.

For girls the problem is more difficult. The majority of outdoor professions entail roughness and lack of suitable companionship.

Amusements.—Many places of amusement are poorly ventilated, overheated, and improperly cleaned. Predisposed individuals should not

frequent them too often. Their amusements should lead them into the open air. Games of all sorts should be cultivated. Alcoholic and sexual excesses are especially dangerous.

Marriage.—Marriage for persons with tuberculous forebears need not concern us if the individuals are robust. If the contrary be the case they should be cautioned about excesses, and the woman if weakly should be warned of the danger of frequent pregnancies.

In regard to marriage of the tuberculous, it is certainly wiser to postpone it until the tuberculous individual has been well for two years. The financial condition should be considered carefully. For the well-to-do, who have no worry about money matters, marriage should be more readily sanctioned than in the poor, in whom anxiety for the wife and babies may prove to be too much for the tuberculous husband or the care of home and children too exacting for the tuberculous wife. Under the latter condition it is certainly wiser to avoid conception.

The danger of infection of healthy individuals who have married tuberculous patients has been much discussed. This danger, though not great, is undoubtedly real. Kissing should not be practised. The danger of infection by coitus is very slight, though Thom ranks it next to kissing. Some explain by this means the greater frequency of infection of wife from husband than husband from wife. Tuberculosis is so rarely transmitted before birth that such danger can be neglected.

Results.—The result of any prophylactic measure in tuberculosis is difficult to determine. The decrease of mortality began in many places before the discovery of the tubercle bacillus, and in London has not decreased any more rapidly since. The results in Norway, where the the strictest measures in regard to notification and isolation has been enforced, are not as yet very startling. The results obtained in Havana during the American occupancy were remarkable. Ascher has made a careful study of the reduction of tuberculosis in Prussia and finds it greater in the circles in which no efforts have been made to combat it.

The first results in State prophylaxis are to be seen in the infant tuberculosis mortality, which in New York, as Biggs has shown, is remarkably reduced, from 0.67 per 1000 of total population in 1883 to 1887 to 0.34 in 1898 to 1902.

TREATMENT

There is probably no chronic organic disease which shows greater tendency to repair and recovery, but this very tendency is fatal for many patients. There is no disease that yields so quickly to such slight efforts on the part of the physician and no disease which progresses so steadily to recovery in the face of so much injurious treatment.

However, these favorable results do not always obtain and the enthusiasm of both patient and physician is often severely tried. The time allotted to the treatment is almost invariably too short, and many patients lack enough persistence to regain their lost health. Another most important factor, really a serious danger, is that many patients

in a few weeks enjoy a feeling of almost perfect health. If a patient felt ill and weak until a full recovery were effected, the percentage of recoveries would be many times increased.

There is no specific for pulmonary tuberculosis. The hygienic-dietetic treatment is almost "specific" for the general condition which, with such treatment, soon equals or even surpasses any state ever reached in health. With the lungs, however, it is a different and a vastly more difficult problem. To change, to arrest permanently, a pulmonary lesion requires not weeks or months, but years. The first part of the time should be passed under careful medical supervision; the latter may be devoted in part to work.

The success of a physician in treating pulmonary tuberculosis depends largely upon his ability to deal skilfully and individually with the physical, psychological, and sociological problems that arise with each patient. His former habits, pursuits, and idiosyncrasies must be carefully noted. He should be told at once that he has pulmonary tuberculosis, for the shock is soon over. The details of the treatment must be gone into fully and the importance of implicit obedience impressed. He should be told that in conscientious observance of minutiæ lies health, and the reason for every rule should be made clear. The duration of treatment is difficult to estimate and varies much with the object in view, *i. e.*, whether improvement, or arrest, be aimed at. Three months is the shortest period from which any permanent benefit can be derived, and this only in the earliest stages. As the disease advances much longer periods are necessary, and two or even three years may be required.

The clothing must not be too heavy. Sensible perspiration and chilliness are equally dangerous. Wraps should always be at hand. Linen or woollen underwear is to be preferred, and chest protectors and chamois waistcoats under the shirt should be strictly forbidden. Water-proof clothing should be avoided during warm weather, but the feet must be kept dry or dried at once on return from exercise. Damp clothing should always be replaced at once by dry. Hats may or may not be worn, but the head must be protected from the hot sun. Corsets should never be worn tight, and for some patients Ferris waists are much to be preferred. The same garment should never be worn for more than twelve hours (*i. e.*, night and day) without thorough airing.

Patients subjected to life out-of-doors and to hydrotherapy soon acquire resistance to colds and to other slight infections—a process now known as "hardening."

The details of the daily life for a patient may be stated simply as follows: 7.00, awake; milk (hot if desired) if necessary; cold sponge; 8.00, breakfast; 8.30, out-of-doors and at rest; 10.30, lunch when ordered; 11.00, exercise when ordered; 1.00, dinner; indoors not over one hour, less if possible; 2.00 to 4.00, absolute rest—no talking; sleep if possible; 3.30, lunch when ordered; 4.00, exercise when ordered; 6.00, supper; 7.00, outside on good nights; 9.00, lunch and bed. Once or twice a week a hot bath, followed by a cold sponge.

Hygienic-dietetic Treatment.—This has long been called the "sanatorium treatment," as it was first carried out in these institutions.

Briefly, it may be said to consist of good nourishing food in proper amounts, of fresh air by day and night, and of exercise and rest properly regulated for each patient.

Fresh air is a most important factor, but this estimate of its importance may be said to rest upon empirical grounds. Fresh air stimulates the hematopoietic functions, the nervous and digestive system, as well as many other organic functions.

The number of hours spent out-of-doors varies for the individual, the climate, and the season. In summer individual peculiarities are of less moment and nearly every patient can spend day and night out-of-doors. In winter, especially in cold climates, many patients find it impracticable to spend more than eight hours out-of-doors. Senseless exposure must be avoided.

The hours out-of-doors should be spent on a comfortable reclining chair or bed on a veranda, never deeper than its height, facing southerly in winter, northerly in summer, well protected from wind, but freely open to the air and well lighted artificially for use after dark. Liegehallen, much used in Germany, where verandas are opposed on the grounds that they darken the rooms, are long, low sheds with open fronts, protected backs and sides, containing windows and so constructed that the flat roof, slanting backward and downward, is at a height in front which equals the depth of the building (usually ten to twelve feet). The patients, at least four feet apart, occupy these shelters throughout the day. Many observers feel that it is wiser in all acute cases, and for many nervous patients, to employ separate balconies or at least divided porches where each patient can be alone at perfect rest out-of-doors.

Of most value in dry climates, tents may become very disagreeable in moderately humid climates and, unless especially constructed, are very poorly ventilated. Notwithstanding many intricate devices for ventilation, the best tent (and the cheapest) is the ordinary wall-tent, on a framework, so constructed that the wooden floor is raised one to three feet above the ground, a space of three inches being left between the sides (boarded up to two or three feet) and the canvas walls, which are so arranged that they can be lifted up to the eaves on all sides. This arrangement changes the tent into a covered veranda. Every tent should be supplied with a small stove.

Many patients living in cities are unable to have access to a balcony, a back yard, or even a roof. Living in apartments or tenements with three or four flights of stairs to climb, it is almost impossible for them to get into the open air. Sitting wrapped up by the open window during the day and sleeping in a window tent at night must suffice.

Sleeping out at night makes little appreciable difference in the immediate results of treatment. For patients who must work indoors it is invaluable. The night air of cities is the purest. Patients who are ill and who may require the services of a nurse (night-sweats, hemoptysis, etc.) should sleep out only under exceptional circumstances. The "lean-to," devised by King, is so constructed that the patients sleep and live out-of-doors on deep, covered porches, extending out on both sides from central living- and dressing-rooms. Bathing and heating facilities,

and a small room, where a patient taken suddenly ill can be moved, are essential to this structure.[1]

Rest and Exercise.—The proper regulation of these is most difficult. It is always wise to err slightly on the side of rest, but many patients return to their former occupations with their muscles so soft and flabby, that relapse is indelibly written upon them.

The rest at first, particularly in febrile patients, and in those in whom the disease has just become manifest, should be absolute (in bed on a private porch). All business cares, letter-writing, study, prolonged or exciting conversations, should be forbidden. For a time the patient should see few visitors. Overexercise *en route* to or on arrival at a health resort is frequent and physicians sending patients away from home should carefully guard against it. At the end of two or more months exercise should be begun in suitable cases and thereafter the problem resolves itself into getting the patient into "condition." Passive exercise by massage may be begun when the patient is still confined to bed, before the temperature is fully normal and when the loss of weight is still marked. It should be carefully watched and cause no fatigue. Active exercise should be begun as soon as possible. It is wise to furnish every patient with a few simple printed rules for exercise, such as the following: (Exercise means walking. Special permission must be obtained before indulging in other forms of exercise.) None for one week after beginning treatment, then ask about it. None if feverish. None if blood in sputum. None if loss of weight. None if fast pulse. Never get out of breath. Never get tried. Never run. Never lift heavy weights. No mountain-climbing. Go SLOW. Exercise regularly and systematically, whether rain or shine. Walk up hill at start so as to come down hill on return. Remember always that you will have to return. Rest one-half hour before and after meals.

Much difference of opinion exists as to the best time for exercise. Some advise it immediately after meals, others between, but all agree that rest out-of-doors before meals is essential. For patients with a weak digestion, rest for one-half hour after meals is often of great value.

Exercise should always be taken out-of-doors, and the best form to begin with is walking on the level either alone or with two or three companions at a rate of two miles an hour, with frequent pauses for rest. It is wise to begin with five minutes in the morning and gradually increase in suitable cases a few minutes each week, until the patient is able to spend four to six or more hours each day on his feet without fatigue. Inclines should not be attempted until the patient can walk one-quarter to one-half hour on the level. In some instances carriage-riding for a definite short time, or a short boat ride, may be allowed when the patient is able to walk but a few minutes. All violent sports should be avoided. Golf (without the full swing), croquet, fishing and hunting (not entailing too much exercise), gentle bicycle riding (on the level), rowing or paddling, skating (for those proficient), skiing, snow-shoeing, swimming (in great moderation), and horseback-riding may

[1] See Carrington, Fresh Air and How to Use It.

be indulged in with moderation, when the disease has been arrested for some months. It cannot be denied that many patients who after recovery do indulge in violent exercises remain well, but more relapses occur from overexertion in sport or games than from work. The amount of exercise that any patient can finally arrive at depends upon his former habits.

There are four chief contra-indications to active exercise: (1) Fever, (2) rapid pulse, (3) blood in the sputum, and (4) loss of weight. While these symptoms cover nearly every case, in a few patients great dyspnœa on the slightest exertion, marked weakness, gastric disturbance, increased cough and expectoration, and increase of physical signs, are also contra-indications to exercise. A subnormal temperature (oral) in winter is of little moment in regard to exercise, when the general condition is satisfactory. A rise of temperature (rectal) to 101°, which after one-half hour of rest falls to 99.5° or lower, does not contra-indicate exercise. The effect of overexertion is often a lowering of the oral temperature of the same day, while the rise does not manifest itself until the second or even the third day. The pulse should be taken before arising and at rest. When at any time it reaches or exceeds 100 per minute, exercise should be taken with great caution and the pulse carefully and frequently noted. A pulse of 110 or over at any time of the day while at rest is a contraindication to any exercise, even dressing. These statements, however, do not refer to a patient who is just convalescing from an acute attack, when some cardiac weakness is expected.

Treatment by "auto-inoculation" consists, as practised at Frimley, in absolute rest in bed (not permitted up for any purpose and even fed) until the temperature is normal. The patient is then put upon walking exercise until he can walk six to ten miles a day without rise of temperature or increase of any symptoms, when he begins work and passes gradually from carrying light baskets, through carrying large baskets, sweeping, chopping, hoeing, painting, digging, and using a wheelbarrow, to do really heavy outdoor work. The results *when carefully controlled at every step* are excellent (see Paterson: Auto-inoculation in Pulmonary Tuberculosis).

Respiratory Exercises.—On the one side all unnecessary movement of the lungs is forbidden, and artificial pneumothorax, a plaster corset or adhesive strapping advocated. On the other, some go so far as to recommend active pulmonary gymnastics in subacute stages. Kuhn has devised an aspiration mask, which retards the inspiration and produces a state of passive hyperemia of the lungs (Bier's treatment). The results are not startling.

The simplest form of respiratory exercise is sighing. Walking up gradual inclines accomplishes the same end. Singing also requires deep breathing and to some may prove injurious. Only those patients with normal temperature and pulse, with incipient or moderately advanced, localized, or slightly disseminated, inactive pulmonary lesions, should be subjected to pulmonary exercises. Active or multiple cavities, old or advanced fibrosis, severe laryngeal involvement and hemoptysis, as well as dyspnœa and palpitation after the exercises, are contra-indications.

Dietetic.—The main object of dietetic treatment is to enable the patient to regain his lost weight, but not to make him a "flabby, breathless mass of inert fat." A patient who eats and digests well is a patient half-cured. The teeth should receive careful attention and be placed in order at once.

The preparation and serving of meals should receive the strictest attention, as the kitchen is the only pharmacy that many patients should know. The meals should be carefully chosen and each planned in relation to the preceding. The physician should carefully scrutinize the diet and lay down broad general rules. It is a wise plan to vary the articles of diet as much as possible and special dishes on special days of the week should be avoided when possible. The table should be attractively arranged and the food well and quickly served (not quickly eaten). Many patients will eat well if the courses follow one another in rapid succession, whereas if long delays occur, cough or fatigue may prevent the eating of the desired amount. To pile up a plate with large amounts and to expect a patient, who especially at first has little or no desire for food, to consume it is a mistake. Repeated helpings until the desired amount is eaten is preferable.

In all acute and subfebrile cases the meals should be served in the bed-room or on the veranda, and when possible a nurse or attendant should be constantly present to supply any wish or whim of the patient and to encourage, to coax, or even to command him to further effort. As convalescence is established the patient should be allowed to come to the table for one meal a day, usually the midday meal. Congenial table companions are almost a necessity to obtain the best results.

The following dietary is one frequently followed, and gives on the whole excellent results: A glass of milk is given before rising, which may be hot if desired and contain a teaspoonful of whisky if the cough is severe and distressing. Beef juice may replace the milk. Breakfast, served at 8 A.M., should consist of fruit, cereal and cream or butter, eggs, steak or chops, with a little broiled bacon, bread and considerable butter, one or two glasses of milk, and a cup of tea or coffee. If deemed advisable a glass of milk or a raw egg should be taken at 10 to 10.30 A.M. Dinner at 1 P.M. should consist of soup, or tasty bouillon or broth, fish or oysters, rare roast beef, mutton, turkey, chicken, and occasionally for a change, if desired, ham, pork, duck, or a little goose; fresh vegetables in abundance and variety; salads with an oil dressing, puddings, jellies, or ice-cream, simple cake. One or two glasses of milk may be taken at the end of the meal and bread and butter in abundance. A demi-tasse of coffee is permissible. All sauces should be prepared with good butter. When prescribed a glass of milk or an egg may be taken at 3.30 P.M. Supper at 6 to 7 P.M. should include cold roast beef, mutton, chicken, occasionally ham, or eggs; a hot meat with vegetables is often very agreeable; bread, butter, tea, cocoa, milk (one or two glasses), jam or fruit (fresh or preserved). A glass of milk at bedtime and another during the night if awake may be given in some cases. Lunches often may be profitably omitted one day in seven, usually Sunday.

The amount necessary for any individual is difficult to determine.

Every patient should be told that he must eat to recover. He may not experience real hunger, but an eating appetite, an appetite that increases as one begins to eat, one which enables him routinely to eat all that he should, is to be most highly prized. When first subjected to treatment the appetite furnishes no index to the state of the stomach or the powers of absorption. All forced feeding should be controlled by examination of the stools for undigested food. Patients who have reached their highest known weight, if it corresponds to the normal weight for age and height, those with chronic fibroid pulmonitis and impeded circulation, those with enfeebled hearts, those with acute processes and very high fever, those whose failure of appetite and digestion is in excess of that caused by the general constitutional weakness, all these should not necessarily enlarge their diet. Many patients chronically overeat, and in a few overeating becomes a fixed idea. Too much is as bad as too little food. In general it may be stated that a patient should consume as little food as is necessary to enable him to gain on an average one to two pounds per week until his normal weight is attained. When the true normal weight is reached the diet should be slowly reduced and the lunches and milk gradually abandoned, if the increase of weight coincides with an arrest of the lesion. Protein excess, especially, should be carefully avoided, while excess of fat is well borne.

Patients with slight fever can usually digest easily all good, plain, wholesome, solid food. Those with high fever may have some difficulty and should receive at first a fluid or semifluid diet and solids be added one by one. It is remarkable to see what foods and the amount that can be digested by some patients with persistent pyrexia. In a few patients the careful use of antipyretics may increase the gastric secretions (Hildebrand) and often enables the patient to eat a good meal. The principal meal of the day should be taken, when possible, during the afebrile period.

Milk, eggs, and meat are the most important foods. It is difficult to overestimate the value of milk, which often enables a patient to regain quickly his lost weight. The amount required varies, but 3 pints for patients on a general diet is a very good average. Some patients with a strong antipathy to milk, by urging and after a fair trial, often overcome it. Small quantities should be used at first in such cases. When hot or cold milk is not well borne it may be treated in various ways. A pinch of table salt or sodium citrate may render the milk clot less firm and more digestible. One or more tablespoonfuls of lime-water, the addition of an aërated water, of a little coffee, tea, or even cognac may enable a patient to take a sufficient quantity. When these fail the milk should be peptonized and taken hot or cold. Koumiss or kefir, possibly the addition of the *Bacillus lactis aërogenes* to the milk, may be tried in case of intestinal fermentation. A considerable quantity of milk may be taken in puddings, junket, porridge, etc. Whey and buttermilk are much less valuable. When milk cannot be taken, the amount of butter and cream may be increased or olive oil added to the diet. A little cheese is of value.

Eggs should be strictly fresh; for most patients six is a safe limit.

They can be taken raw, as most prefer, or cooked. In some patients the yolk of the egg causes gastric distress or even purging; these should take only the white.

Meat is of importance and should at first be eaten at two meals. Beef and mutton are to be preferred, and, while the latter is more readily digested, the former proves from experience the better food. Chicken and turkey, while of less value, are better than duck, goose, or fish. Twice-cooked meat should be avoided. Rare meat is better than well-done, and raw meat is held by some as the best, combining the maximum of useful results with the minimum of digestive effort. Raw meat (beef) may be given as scraped-beef sandwiches or in little balls, rolled in chocolate, when the taste is disagreeable, as it needs no mastication. The muscle plasma, ordinarily called beef juice, is of considerable value. The meat should be as fresh as possible, and often the cheapest and toughest cuts (brisket, rump, etc.) yield the most juice. Many of the meat powders, containing three or four times as much nourishment as a similar quantity of meat, and easily digested, are unpalatable. Blood, once held in high esteem, is now little used on account of the repugnance many patients have to it. Meat extracts, bouillon, and meat broth, though containing little nourishment, often stimulate a flagging appetite.

Fats.—These are of great importance to the tuberculous. Hutchinson has affirmed that by a study of the amount of fat eaten it could be determined which members of a family would succumb to tuberculosis.

The best form in which to administer fat is undoubtedly milk and its derivatives, butter and cream. Cod-liver oil is much less used than formerly and many patients cannot take it. Combined with malt, aromatic oils, or bitter tinctures it is more palatable. It should never be given during warm weather nor when high pyrexia is present. There is no objection to a good emulsion whose formula is known. Olive oil, well taken by some patients, is valuable. Many fishes contain much oil, *e. g.*, sardines and salmon. The stools should be examined whenever fats are administered, to prevent excess of administration.

Water should be taken freely (1 to 2 quarts daily) between, or preferably hot and one hour before meals. Coffee, tea, and cocoa may stimulate the organs to take up more nourishment.

Many prepared foods have been used with apparent success. Animal food rich in nitrogen is poor in phosphorus and vegetables supply this deficit. Fruits and nuts are of value and the grape cure in France has been recommended.

Institutional Treatment.—To institutional treatment the proof that pulmonary tuberculosis is curable is largely due. For many years the sanatorium was looked upon as the central point in the struggle against tuberculosis, but more recently it has become evident that only a small fraction (possibly not over one-tenth) of the tuberculous patients could gain admission or leave home to undergo treatment at these institutions.

Hospitals.—The hospital, of great value in prophylaxis, is of less aid in treatment, which in most general hospitals is insufficient, illusory, and dangerous both to the tuberculous and other patients.

Dispensaries.—The dispensary affords the best treatment for those patients (almost 80 per cent. of all) who, still able to work, must do so and remain at home. It should coöperate with all existing charities, and should be open at a time convenient for working patients. The trained nurse, who should possess tact, energy, interest, and ability, is indispensable. She visits the home of every new patient, makes a careful detailed report of the social condition, and revisits old patients to see that the instructions are properly carried out.

Sanatoriums.—The objects are twofold, healing and educational. In Germany the insurance sanatoriums and those for the poor aim more to restore the working capacity than to arrest the disease permanently. The sanatorium should aim to arrest every patient, and, if possible, to do so in a period of residence of six to twelve months. However, many cannot be brought to arrest, but for these patients the educational influence is of great value and many ultimately recover by means of the knowledge so acquired. On leaving the sanatorium they teach how to prevent infection and still foolish alarms.

Selection of Patients.—This is most difficult in some instances and depends mainly upon the prognosis. Patients under fifteen years of age should be in special institutions with educational advantages, and those much beyond fifty rarely fully recover. In general all patients with incipient disease, and many in moderately advanced stages, are suitable for sanatorium treatment. Far-advanced or hopeless cases should not be admitted. Patients with tuberculous complications, or with albuminuria, diabetes, a persistent diazo reaction, chronic diarrhœa, melancholia, profound neurasthenia, or pregnancy, are not acceptable. Patients with slight tuberculous complications, such as slight thickening in the posterior interarytenoid space, slight superficial ulceration of one cord without infiltration, or fistula-in-ano, often do well. Former patients who have relapsed often do badly. Patients with pronounced symptoms out of proportion to the physical signs, with marked, persistent tachycardia or pyrexia (at home and at rest), those who have steadily declined since onset, with continuous loss of weight in spite of hyperalimentation and those with marked dyspnœa on slight exertion are not suitable. The aims of the institution, however, determine the class of patients it should receive.

For institutions which are anxious to obtain good results, the only safe plan is to have a large waiting list, to keep each patient some weeks under observation or to select the most suitable from the list, a practice which works much hardship upon the patients, and is not to be recommended. The sanatorium should endeavor to exclude all non-tubercuIous patients, and every patient in whose sputum tubercle bacilli are not or have not been found should be subjected to the tuberculin test.

Treatment.—The treatment of patients in a sanatorium must be individualized and "hospitalization" avoided. Firmness, not dogmatism, should be aimed at in connection with all rules, as well as great common sense. The patients act in many instances like children, and the responsibility that rests upon the shoulders of a true sanatorium physician is

not light. The following paragraphs refer mainly to afebrile patients, able to be up and about:

The Daily Life.—On admission the patient should spend at least two weeks in the infirmary or reception cottage, where he is under close and constant obervation and is taught many things that usually require months to learn at home. It is a grave mistake to watch so long over the patient that he feels he need no longer consider whether for him an act is "right or wrong." This weakening of self-control may result disastrously when the patient returns to his former surroundings, and is in a certain sense one of the objections to sanatoriums and a great argument for home treatment.

Strict rules are very necessary, but should be as few and simple as possible. Smoking at stated intervals for selected patients may be indulged in, but only out-of-doors, and inhaling should be forbidden. All patients should be in bed with lights out at from 9 to 10 P.M.

Visitors should not be allowed to interfere with the daily routine, but at some time during each patient's stay at the sanatorium some member of his family should visit him to see what he should do on returning home. Provision should be made for only one or two visitors at any one time. No visitors suffering from colds or influenza should be admitted.

Amusements, Classes, Work.—In all sanatoriums the time passes slowly for many patients and every opportunity to encourage idleness is afforded. This tendency should be strongly combated by suitable work, classes, or amusements. A good library with the current magazines, and a piano for those patients who are allowed to play, are important. Photography and sketching are useful, but nature study is far more valuable than any of these. To arouse or instil a love of birds, flowers, geology, or some kindred subject, an interest which the patient will carry with him through life wherever he goes is of extreme value. Every patient if possible should leave the sanatorium with an outdoor hobby. For many nature study has no charms, and for these arts and crafts of wide variety should be provided. Suitable useful work is a great mental relief to many patients who envy the man who is allowed to do most.

Work at a sanatorium depends much upon the class of patients accepted. Many charitable or semicharitable sanatoriums require all patients to do some work, which, however, should be done leisurely and never under tension. Patients at work need very careful medical supervision, and malingerers often have to be overlooked for fear of injuring an honest patient. Ample time for rest should be afforded.

Length of Stay.—This varies from an average of three months in the insurance sanatoriums to one to three years in some private institutions. No permanent benefit to the lungs can be hoped for in less than three months. In fact, more patients require four or five years to attain a permanent arrest. For those dependent for their livelihood upon their own exertions, six to twelve months should be an average length of stay, but on discharge the patient should be frankly told that the next two years are the most dangerous for him. If he return to work, he

must work and take care of himself, and he cannot usually play as well.

In some instances it is very difficult to decide when a patient should leave the sanatorium. As long as occasional attacks of fever, a persistently rapid pulse, and fatigue after slight exercise are present, the patient's position is still insecure. When, however, the patient can work or take considerable exercise, needs no longer a forced diet to maintain his weight, has been apparently well for three or four months, he may safely consider returning to his home.

Modifications.—Day sanatoriums, night sanatoriums, tuberculosis classes, day camps, are all of importance.

Home Treatment.—The immense majority of all tuberculous patients (98 per cent.) have to be treated at home. At least 75 per cent. of those who seek "sanatorium" or climatic treatment return to their homes long before the disease is permanently arrested. The treatment pursued in many of the "open" health resorts is, for those who can afford it, treatment in their homes, and many of the objections urged against home treatment apply to this.

Treatment at home is less expensive, does not entail residence in a hotel or boarding-house or acclimatization after return to work; precludes separation from the family and friends, fatigue of travel, homesickness; does not break up business arrangements in the same degree, and in fact possesses every advantage, according to Flick, but climate. Further, "at present instead of finding the best trained experts for the treatment of tuberculosis in health resorts, with some notable exceptions, we find them in the large centres of population; and the opportunities for getting expert treatment are perhaps better in large cities than in some of the health resorts" (Flick).

A most important factor is the training of the family. When this is once accomplished the adjustment of the future life is more readily obtained, more consideration is afforded both by friends and by the family, and permanency of the results is better assured.

It requires more moral stamina to sit out alone in a damp, cloudy, foggy climate than to do so surrounded by pleasant companions in a bright climate. The care and worries of home life are never fully lost. The mother cannot neglect her children nor can a merchant calmly neglect his business. The anxiety produced by sickness cannot be avoided at home. A selfish, exacting family is an indication for a change of residence, and no patient who has long borne all the burden of the family should be allowed to remain at home. These disadvantages of home treatment are neither few nor slight, but once met and overcome, the permanency of the results is at least theoretically better.

When possible the patient should move to the healthiest locality in the region. A change to the country or at least into the suburbs for a year is advisable. The house should stand well back from the street and not too near the neighboring houses, should have a sunny exposure, and, if possible, be at an elevation of 300 to 700 feet. The neighborhood of factories, gas-houses, power-houses, etc., should be avoided.

A sunny room, 12 x 14 feet or larger, with a ceiling 10 feet high, lighted by electricity, heated with hot water or steam, with two windows, or a window and a door opening out on a sunny balcony protected on one side with glass on which the bed may be rolled, makes an ideal place. These conditions, however, can rarely all be obtained, and many shifts for the "cure" must be made. A tent in the back yard or on the roof, a bay window or even a well-ventilated room may have to suffice for a time. The problem of good food with the poor is more serious than that of fresh air. A few weeks' residence at a sanatorium or the services of a trained nurse well versed in the treatment of pulmonary tuberculosis for a few weeks is of much importance.

Climatic Treatment.—The value of certain climates has in recent years been called into question and today rests largely upon personal belief and experience. Much has been written and little proved. There are localities differing widely in every climatic element in which man does well—why, we often cannot say. Many climates unquestionably exert some influence upon man in health.

There is no specific climate for pulmonary tuberculosis, and a good climate alone is of little avail. Without doubt many of the effects attributed to climate can be ascribed to change of climate. Change from a "good" to a "bad" climate often produces excellent results. It is rarely advisable for a patient to remain in any climate without change for more than eight or nine months.

The objects of climatic treatment are to furnish a complete change of environment, to withdraw the patient from the influences under which he contracted the disease, to subject him to a climate which will promote healing in the lungs, by increasing the activity of the digestive functions and thus stimulating nutrition, by improving the tone of the nervous and circulatory systems, either by invigoration or protection, and by lessening exposure to secondary infections. Further climatic treatment may have for its object palliation of distressing symptoms in patients whose disease may not prove fatal for months.

The ideal place for a patient with pulmonary tuberculosis should possess purity of air, a dry, porous, salubrious soil, good potable water in sufficient quantities, good sewage disposal, relative protection from wind, and such a temperature that the patient can spend hours out-of-doors without discomfort. Abundant sunshine, infrequence of fogs, the persistence of snow throughout the winter, are all of value.

Wind has been described as an etiological factor in pulmonary tuberculosis, but its chief action is, no doubt, due to keeping the population indoors where with all crevices carefully closed the ventilation is poor. It greatly purifies the atmosphere, although in excessively dry climates it creates much dust. Forests and vegetation prevent dust, protect against wind, and render the climate slightly more equable.

Young persons usually meet high heat demands well, those past fifty years less certainly, while older individuals fail to meet them. Younger, fairly robust or robust patients, therefore, demand a climate of invigoration, which is cold, dry, variable (a diurnal variation of 20°) and more or less elevated, while older, more or less delicate persons

need most frequently a climate of protection which is warm, moderately dry, equable, sheltered, and lying usually at much lower levels. Large eaters, often somnolent in summer, usually stand cold well. Patients susceptible to chilblains, and to Raynaud's disease, may do remarkably well in cold climates.

Symptoms have long been used as a guide in the choice of climate. The increase of cough and even of expectoration that occurs on change to a cold climate was long advanced as an argument against cold. More recently it has been clearly recognized that the increased nutrition amply affsets this exacerbation of cough, which in patients suitable for such climates soon ceases. A dry climate is suitable for free secretion and a sea climate for scanty secretion in bronchitis, but the same does not necessarily hold in pulmonary tuberculosis (Lindsay). A tendency to hemoptysis need not be considered unless in a patient with extensive cavities, when high altitudes are contraindicated. Patients with chronic catarrh should avoid windy places (Weber); those with asthma should go to moderately elevated localities if young, to warm resorts with slight elevation if older.

Acute pulmonary tuberculosis is a contra-indication to change of climate. A temperature of 99° to 100° F. in the morning, rising to 101° to 102° F. in the evening, precludes travelling. When the temperature falls to normal in the morning a change may be considered. Persistent tuberculous diarrhœa, extensive laryngeal invasion, pneumothorax, advanced nephritis, marked dyspnœa with cyanosis, cachexia, and grave diabetes are complications that usually contra-indicate change of climate, although life in many cases may be prolonged and suffering alleviated by change from a colder to a warmer clime. It should never be advised unless the patient can obtain every comfort. In general, patients in acute stages should be kept at home. Robust patients in subacute stages, or with chronic ulcerative disease within certain limitations, may be sent to any climate. Patients with advanced fibroid disease, delicate patients with subacute or chronic ulcerative disease, need a climate of protection, neither too cold nor too high, but those in early stages will do well in almost any climate.

The mental characteristics, habits, and surroundings of the patient at home must be considered. The pecuniary condition is of much importance. No patient should seek health in an open resort without $250 or sufficient for a six months' residence besides his railroad fare. The opportunities for work at health resorts are slight, as the field is already overcrowded. The practice of sending patients to health resorts with the advice to live out-of-doors, to exercise freely, and to consult no physician is criminal. It is inexcusable to send patients to places of which the physician knows little or nothing either in regard to the expense, the accommodations, or the medical fraternity. A few wise, frank words of good medical advice *on arrival* may prevent a serious relapse or fatal illness. Great caution should be exercised for the first two or three weeks in a new climate.

Deserts.—The chief characteristics of a desert climate may be said to be purity of air (considerable ozone), dryness, a maximum amount

of sunshine (and of light), great but constant variations of temperature between day and night, and slight precipitation resulting in few cloudy days, lack of vegetation, and much dust. The best-known desert climate is that of Egypt. Cairo should be avoided and the patient should go at once to Mena House, Helouan, Luxor, or Assouan. Weber opposes the Nile trip. The oasis Biskra in Algeria has been recommended. The United States, however, possesses the most varied desert climate with an elevation varying from sea level to 6000 feet above in Arizona, New Mexico, Utah, Southern California, and Colorado.

Marine Climates.—A marine climate is characterized by purity of air, an equable temperature, high humidity, high barometric pressure, great luminosity, and complete absence of dust and bacteria. For the majority the marine climate may be said to be sedative as well as tonic. Sea bathing is not advisable, but douches and sponging with sea-water may be employed.

Sea voyages were formerly much recommended, but in recent years have fallen, and for the majority of patients justly so, into disuse. The position of ship's surgeon for a tuberculous physician ought to be recommended only under the most favorable conditions.

High Altitudes.—"High altitudes" may be said, at least for therapeutic purposes, to begin at 4000 feet elevation, while those above 7000 feet need little consideration. The characteristics of these are low barometric pressure with consequent reduction of oxygen, purity of air, low humidity, much sunshine of great intensity, a soil usually dry and porous, and great difference between the temperature in sunshine and shade. The effect of these factors upon the human organism has long been studied and the results of this research are very variable and in many instances contradictory. The thorax in time becomes larger (1 to 3 inches) and more mobile, depending on age, and to some extent upon exercise. The lungs develop a capacity to secrete oxygen from the alveolar air into the blood. Nutrition is stimulated and the increased oxidation takes place at the cost of the carbohydrates, with a consequent lessening of the fatty tissue. The appetite and weight are usually increased. Marked nervousness at times results.

The pulse at first and for many months in some is quickened and the increase after exercise is more noticeable than at lower levels. At first palpitation may occur but the blood pressure is little changed. The effect upon the blood has not yet been finally settled, but an increase in the number of erythrocytes and of lymphocytes in the peripheral circulation takes place. During the first few weeks (usually three) at high levels the erythrocytes gradually decrease, but later a real increase has been noted.

The effect of high altitudes upon patients with pulmonary tuberculosis is difficult in many cases to foresee. Great caution in regard to rest, exercise, and food should be practised for four or five weeks. Medical advice on the arrival in a high altitude is of the utmost importance. Many patients after recovery return from high levels to low with no ill results, but some find they must reside permanently at a considerable elevation. There are four reasons why a patient should go to a lower

elevation: lack of improvement, cyanosis, and difficulty with sleep or breathing (Bullock.)

The indications for treatment in high altitudes are far from exact. The general condition is of great importance, and a constitution capable of some resistance and organs capable of increased nutritive and oxidizing work are necessary. If the foregoing conditions be not fulfilled, or if albuminuria, severe diabetes, pronounced emphysema, grave anemia, nervousness, rheumatism, or severe gout be present the patient should not seek health in high altitudes. Marked arteriosclerosis, cardiac dilatation (unless very slight), nervous derangements, persistent tachycardia, pronounced aortic or mitral regurgitation uncomplicated or complicated by pleural and pericardial adhesions, forbid this treatment.

The most famous resorts in high altitudes are the Alps, the Rocky Mountains, and the Andes. The last is little used for patients in the northern hemisphere. The Alps are colder, have much more snow, more precipitation, more vegetation, are more frequented by healthy individuals, but offer much less opportunity for future employment than the Rockies. The latter are more suitable for weaker patients, have more sunshine, more wind, and more dust. Suitable accommodations are less expensive in the Rockies. Smelting towns should be avoided.

Many health resorts lie at a moderate altitude (1000 to 3500 feet), and it is still unsettled at what elevation the physiological phenomena attributed to this factor are first apparent. They cannot be said to have any peculiarly characteristic climate, but vary according to their latitude, or to their proximity to sea or desert. The only feature they have in common may be said to be purity of atmosphere. The best known of these resorts in America are the Adirondack Mountains, the regions about Asheville, about Liberty (N. Y.), parts of Maine, the Muskoka region, St. Agathe, Quebec, etc.

Balneotherapy.—The effect of balneotherapy upon pulmonary tuberculosis has long been questioned. The climate of many of the spas, found of avail in this disease, is often mountainous and excellent, but the duration of the treatment, three to six weeks, is too short for such a chronic disease. The waters of saline springs are of value in the catarrh of quiescent, torpid, and anemic patients.

Post-discharge Treatment.—On the return to the active duties of life the patient should have made clear to him that the struggle is not over and will not be over for four or five years. On discharge from treatment he should be given a card which contains his proper weight for his height and age, the lowest limit of safety, lists of suitable occupations and sports, brief statements concerning hours of rest (in bed), sleeping out, the normal pulse and temperature range, etc.

For months he should exercise the greatest care and live as nearly as possible the life he has been pursuing. The cold sponges, eight to twelve hours in bed every night, strict avoidance of persons suffering from colds and influenza, working only in well-ventilated rooms, avoidance of dust, of cramped positions, of fatiguing occupations, especial care about the diet and bowels, are all matters of great importance. Eight to ten hours a day in the open and sleeping in a well-ventilated

room are sufficient for most patients, but on return to work in rooms, more or less poorly ventilated, sleeping out becomes almost a *sine qua non* of continued good health. Many devices have been employed to approximate these ends. A few patients find that permanent residence in a good climate is often necessary to enable them to work. Whenever possible the full quota of work should not be attempted at first, but gradually attained. Light work indoors is better than heavy work out-of-doors, and easy work in a home climate is far better than severe work in a health resort. The agricultural colony should be closely associated with the sanatorium to achieve the best results.

Symptomatic Treatment.—Fever.—This coincides in most cases with the treatment of the disease. Every patient should have fully explained to him the ordinary causes of fever, such as excitement and overexertion. He should, further, be told that slight coryza, simple angina, constipation, and diarrhœa may cause fluctuations in his temperature and that a subnormal temperature, when every other symptom is favorable, needs no treatment; that the indications for rest depend not upon the low morning, but upon the afternoon or highest temperature, and that the highest temperature of one day decides what he should do the next. If fever occurs during the menses the patient should remain at rest, or, better, in bed for the first day or two. A rise of the morning or minimum temperature, even if it does not exceed 99° (oral), indicates absolute rest, and if it reaches 99.5°, rest in bed for several days may prevent a long and stubborn attack. Patients especially prone to fever should avoid heated discussions, and prolonged visits should not be allowed. Exciting games, many visitors, and exciting novels, writing many letters, or attempting to transact business should all be forbidden.

Rest.—This has long been adopted as the most efficient method of combating fever in pulmonary tuberculosis. In many instances rest can be enforced only when the patient remains in his room with wide-open windows. To employ rest properly, however, it should always be taken out-of-doors, and a small, well-sheltered porch upon which the bed can be wheeled from the bed-room is ideal. The amount of rest required varies directly with the degree and persistence of the fever. A slight rise of temperature in a patient previously afebrile should always be treated by rest in bed, out-of-doors if possible, when the temperature reaches 100° at any time of the day. A few days' rest in bed will usually suffice to bring the temperature down to normal, but the patient should not be allowed to get up until his temperature has been 99° or lower for three consecutive days. A rise to 99.5° (oral) would contra-indicate all exercise except dressing, although permission may in many cases be given to go to the table for meals. In a few patients the fever persists until they are put upon a "typhoid regime" and not permitted to feed themselves or go to the toilet.

In some cases it is impossible to get the temperature below 99.5° to 100° every afternoon, even after prolonged rest in bed. If such a patient becomes depressed, loses his appetite, has a poor digestion, and begins to lose the weight previously gained, and if sleeping out at night does not reduce the fever, he should be allowed to sit in a reclining chair on

the balcony for half an hour each morning, but should not dress. If this does not raise the temperature the time may be increased, or he may get up in the morning for a short time. Some patients unquestionably improve more rapidly under this treatment, and those with digestive trouble are often helped by this plan. Short walks or drives may assist greatly in the recovery. However, if the minimum temperature is high, *i. e.*, if the temperature is continuous, great care should be exercised. All patients whose temperature reaches 101° or over should be kept in bed for weeks if necessary or until, after a consultation, all hope is abandoned.

The treatment of acute fever varies with its cause. If due to some non-tuberculous intercurrent disease the treatment usually accorded that disease should be followed, but only within certain limits. If possible the disease should be treated in the open air, and in any case the patient should be put out-of-doors as soon as possible and good ventilation insured while indoors. If the acute attack is tuberculous in origin the patient should be kept continuously out-of-doors.

Hydrotherapy.—This should be employed with great caution and carefully watched. No hydrotherapeutic measures should ever be employed which exhaust the patient, and as a rule only those which do not necessitate moving him should be frequently and continuously used. Sponges, at first with water at 98° and later, when more accustomed to them, with water as low as 50° or 40°, are often refreshing. A salt sponge in the evening, followed by an alcohol rub, refreshes the patient and frequently induces sleep. If the patient is weak, alcohol may be added to the salt-water and not used separately.

Dietetic.—The diet depends upon the cause of the fever and the state of the digestion. In acute fevers not due to the tuberculous process the diet should be fluid if the fever is high. The chief dependence should be placed upon milk, either plain or diluted. It may be well to restrict the diet for several days, notwithstanding some loss of weight.

In chronic fever, food should be pushed to the limit and solids given freely. Fever rarely abates while the patient is losing weight and the necessity of eating should be impressed upon him. Idiosyncrasies should be given due regard and the patient forced to eat nothing he has an antipathy for, with the exception of meat, eggs, and milk. In high fever and when little food is taken it should be given regularly during the night if the patient is awake. In all cases a glass of milk or an egg should be taken at night if the patient awakes. Fats and carbohydrates should be supplied plentifully.

Medicinal.—Antipyretics should not be used until the fever has persisted for two weeks and are of little avail unless the patient is at rest. In some cases when a rise of temperature just before a meal prevents the patient from eating, or a rise at night prevents sleep, a judicious use of antipyretics often helps the appetite and prevents the insomnia. The most satisfactory and the least depressing antipyretic is pyramidon. Two grains given in capsules, at 9, 10, and 11 A.M., are often sufficient to bring about the results before mentioned. Five grains may be dissolved in a tumbler of water and sipped through-

out the day. In some patients profuse sweating follows the exhibition of the drug in capsules, but is less likely to occur if taken gradually in the watery solution.

Besides pyramidon many antipyretics have been suggested. Antipyrine, 3 gr. (0.2 gm.) q. 4 h.; aspirin, 5 gr. (0.34 gm.) t. i. d.; acetanilide, phenacetin, and many others have been recommended.

A tablet compound of acetanilide, gr. 2 (0.13 gm.), camphor monobromate, gr. 0.5 (0.03 gm.), and caffeine citrate, gr. 0.5 (0.03 gm.), often reduces the temperature, and even when failing to do this may prevent the disagreeable chills and sweats which often accompany it. The use of arsenic is said to prevent chills. The antistreptococcic serums have seemed to benefit few patients.

Coughs.—*Prophylaxis.*—A patient with persistent cough should be warned against all acts of overexertion, such as rapid and loud talking, laughing, singing, rapid walking, running, and hill-climbing. He should avoid all irritants, including very dry air, vapors, smoke, dust, and drinks. Tobacco may have to be forbidden. The patient should have fully explained to him that it is not necessary to raise the sputum from the lungs, for cilia are provided for that purpose, and every cough is an act of exertion and may further injure the lungs. Cough often begets cough and a tendency once repressed may mean escape from a violent attack.

If the cough is due to the pulmonary lesion it must be controlled by appropriate treatment in many patients in order to prevent the discomfort or complications that may arise. Deep breathing, ten slow deep inspirations followed by slightly stronger expirations, Cornet found useful. Holding the breath may help. Rest in bed for a patient suffering while up and about with excessive cough is very effectual at times. Change of position has often a marked effect, and a patient who while in bed cannot eat when he sits up, on account of cough, should assume this position for a longer or shorter period, one-half to one hour, before meals. Cough due to pleurisy or fever is relieved by appropriate treatment, *e. g.*, strapping the side or the use of pyramidon.

Sips of cold water, an occasional bit of ice, sugar-water (irritating to some), a bit of orange or its juice, some form of lozenge, such as glycerin, slippery elm, mentholated, marshmallow, licorice, lactucarium, Iceland moss, malt (bonbons), althea, gum arabic, may each prove useful in some cases. Too free use of any of these lozenges may prove diastrous. Counter-irritation has long been employed. A blister or painting with tincture of iodine under the clavicle on the affected side may give some relief. Suitable dietetic treatment may greatly lessen the cough, and the effect of cod-liver oil is well known.

An effectual *morning cough* should never be checked, but may be aided by the use of a cup of hot water with or without a teaspoonful of brandy or 20 drops of the aromatic spirit of ammonia and 5 gr. each of sodium chloride and sodium bicarbonate. Hot milk may be used instead of water.

Night Cough.—Many patients who cough on change of position experience some trouble on lying down. Hot water or milk one-half

hour before bedtime may lessen this. The bed should always be warm. An incessant cough that prevents sleep must be checked, for a time at least, at almost any cost, and when other measures fail a sedative cough mixture should be used. The cross-binder may afford considerable relief and is worthy of trial.

The attacks of *paroxysmal cough* are often difficult, but most necessary to check. Absolute rest in bed may bring relief. A few crystals of menthol vaporized in a spoon over a match and inhaled, and the inhalation of a few drops of chloroform and various mixtures, may be tried. Morphine should not be injected hypodermically; a few drops of laudanum upon the tongue may control the attack. The continual use of the respirator may help.

The *emetic cough* is serious. Here, too, rest in bed for a time and in all cases avoidance of exertion after meals, may be beneficial, but limiting the fluids, especially hot drinks, at meal-time, and taking hot water as advised for the morning cough half an hour before meals and coughing up the collected secretions before meals, is often sufficient. In some instances the odor or the taste of the sputum causes nausea or irritates the pharynx. Here, besides deodorizing inhalations, the pharynx may be painted with various solutions (antipyrine, 20 per cent.; cocaine, 5 per cent.; sodium bromide, 20 per cent., etc.). The wheezing so often complained of, especially at night, may be relieved by expectorants or by the use of belladonna, cannabis indica, or stramonium.

Intratracheal injections and inhalations are chiefly of use in the treatment of cough and expectoration. Injections of menthol, creosote, guaiacol, iodoform, oils of eucalyptus, thyme, and cinnamon in olive oil, have been used with success in cough uncontrollable by other methods, and seem at times to render the sputum more fluid.

Inhalations often markedly benefit the cough, especially when the irritation is in the larger bronchi. The oronasal respirator (Yeo), which can be worn continuously, is probably the best means of administering vapors. A croup kettle, the simple atomizer, or a tin vessel with a towel for a cone, answers for hot steam inhalations. The following simple formulæ may be tried:

Sprays.—Menthol (1 per cent.) and oil of pine (1 per cent.) in albolene, tannin (2 per cent.), or liquor ferri subsulphatis (10 to 20 per cent.) in water.

Inhalations.—Croup kettle, etc. Compound tincture of benzoin (1 to 128 of water), carbolic acid (2.5 per cent.) in water, or creosote, eucalyptus, oil of pine, or oil of turpentine.

Oronasal Respirator.—Equal parts of creosote and spirit of chloroform; eucalyptol and ol. pini sylvestris, āā ʒiij, spirit of chloroform or alcohol, to ʒj (10 to 20 gtt.); or fluidextract of conium, 1 to 3 minims in alcohol.

There are certain periods when the administration of *sedatives* seems to be choice of the lesser of two evils, and many of the milder ones may be used continuously for long periods. Cherry-laurel water, syrup of wild cherry, and hydrocyanic acid, usually in combination with other drugs, are of value. Chloroform, chloral, and the bromides may prove

useful. Indian hemp, belladonna, hyoscyamus, gelsemium, aconite, have been advocated and may be carefully tried.

The routine administration of sedatives should be avoided if possible, as the respite from cough obtained by the use of opiates is bought with a price. Morphine should be used only in the terminal stages unless all other sedatives fail to give relief. It should be administered by mouth as a powder, or in fluid until all hope is lost, then hypodermically. Of the opiates, codeine, gr. $\frac{1}{4}$ (0.016 gm.), heroine, gr. $\frac{1}{12}$ (0.006 gm.), dionin, gr. $\frac{1}{4}$ (0.016 gm.), are the best. The smallest possible doses should be given, and it is a good plan to change from one to another. Dover's powder (gr. v to xv), or a few drops of the deodorized tincture of opium, often help when codeine and its allies fail.

Expectoration.—*Exercise.*—When permissible, walking slowly on the level, up slight gradients, and up stairs, all aid expectoration materially. The exertion of dressing and undressing often facilitates it unnecessarily and undesirably. Simple respiratory exercises, taken between meals, or while walking, such as slow inspiration and expiration, with concomitant movement of the arms up and down, may help in raising the sputum.

Position.—Change of position often greatly facilitates the expectoration and should be more frequently employed therapeutically. Massage of the chest may aid mechanically and helps the circulation.

Inhalations.—These often loosen the expectoration and are in some instances almost specific for the fetor. The steam moistens the air of the room, and when saturated with balsams or carbolic acid renders the sputum less tenacious. Inhalations of creosote under a tent, or of carbolic acid (2.5 per cent.) from a vaporizer or croup kettle, are very efficacious.

Medicinal.—The value of hot drinks is marked. The ammonium salts (chloride, gr. v to x [0.3 to 0.65 gm.]; carbonate, gr. ij [0.15 gm.]) or the aromatic spirit of ammonia are probably the best expectorants for general use. Squill and senega are of value. Ipecac, apomorphine, and pilocarpine are of less value. Citric acid or its sodium salt may be tried when other means fail. Potassium iodide, gr. v (0.3 gm.), and hydriodic acid in syrup are often helpful. Digitalis and camphor, when the heart is weak, are often of considerable value. To lessen the expectoration as well as the cough, creosote and its derivatives, are excellent. Dilute hydrochloric and sulphuric acids and atropine should be tried in distressing cases.

Hemoptysis.—When conscientiously put to trial no method of treatment, as yet suggested, is helpful in every case. The first duty is to calm the fears of the patient and his family. In an initial hemoptysis only a cursory examination (inspection and auscultation) of the front of the chest should be made until the patient is up and about.

The patient should assume at once a semirecumbent position, which favors the gravitation of the blood to the limbs and facilitates expectoration. The room should be well ventilated and cool (45° to 60°), and sufficient, but not too much, covering should be used. Talking should be forbidden, only the necessary attendants allowed in the room, and the cough repressed as much as possible. Small pieces of ice held

in the mouth often aid in this, but too much ice may upset the stomach. An ice-bag should be placed over the heart. Application of cold to the genitals has been suggested. In severe attacks the patient must be made to lie absolutely quiet, and not allowed even to feed himself.

The diet in slight or moderate hemoptysis should be non-stimulating and cold or warm (never hot). Fluids should be restricted, and all alcohol, tea, coffee, or chocolate forbidden for some days. Acids are very grateful to many patients and help quench the thirst, but prolong the coagulation time. Six glasses of milk (40 to 50 ounces) and 6 raw eggs for the first twenty-four hours is the best diet. This should be given at frequent intervals and in small quantities, but not begun until several hours after the hemopytsis. The second or third day it is well to add beef juice, jelly (gelatin), and meat sandwiches (scraped raw meat if possible), and then go back to a solid but restricted diet as soon as possible. In severe hemoptysis it is wise to restrict the fluids greatly and to place the patient for several days on a very limited diet.

To limit the volume of blood in the lesser circulation many methods have been employed. In the first place the skin vessels should always be protected against cold, especially sudden cold, *e. g.*, such as changing sheets in a cold room. Ligatures can be applied to three limbs at a time and changed in rotation, one every twenty minutes. The pulse should not be obliterated and the ligatures should be loosened gradually and not left on too long.

To increase the resistance on the proximal side of the point of rupture would necessitate constriction of the pulmonary vessels. The wall of the bleeding vessel, as has been mentioned, is always diseased, and it is futile to base any treatment upon producing any change in the diameter of the affected vessel. Consequently, we can hope to gain little by drugs producing vasoconstriction (ergot). Adrenalin in slight, oozing hemoptyses by subcutaneous injection or by mouth is held by some to be of value. Intratracheal injection (40 minims of a 1 to 1000 solution in one and a half drams of water) may prove more effective. Recent experimental work has shown that pituitary extract (infundibular portion) may be of value injected into the muscles in doses of 2 cc. until the systolic blood pressure rises to 150 mm.

The nitrites have long been used. Flick controlling his results by observation of the accentuation of the second pulmonic sound uses the alcoholic extract of nitroglycerin in 0.5 to 1 drop doses every one-half hour when necessary. Francis Hare first called attention to the value of amyl nitrite in hemoptysis, which, when exhibited in doses sufficient to produce its physiological effects, is of marked benefit in some cases and should always be used at once. If it fail to act advantageously when thus used it should be discarded. Pearls of 3 or 5 drops may, if useful, be put safely into the hands of the patient.

Sodium nitrite lowers the systemic pressure, and if the pressure in the pulmonic system vary directly with that in the radial artery (a point not yet proved) this nitrite would ensure a lowered pulmonary tension for two or three hours. The great difficulty lies in the fact that it is difficult to tell just when to repeat the dose. It is dangerous to

lower the blood pressure too much and unwise if beneficial not to lower it enough. Observation of the accentuation of the second pulmonic may be of value in some patients, but to overcome these difficulties more surely the systolic blood pressure should be taken every two hours and the doses ordered accordingly, aiming to keep the tension within certain limits. Practically, it is wise if the patient is very nervous to administer codeine, gr. $\frac{1}{4}$ (0.016 gm.), or morphine, gr. $\frac{1}{8}$ (0.008 gm.), hypodermically, and possibly with it sodium nitrite, gr. j (0.065 gm.).

Hemoptysis frequently occurs in the early morning hours and the patient awakens spitting blood. This may be due to variations in the pneumonic pressure which when sudden are probably more dangerous than a steady high pressure. To prevent these variations as much as possible and to equalize the blood pressure, it is well to give morphine hypodermically between midnight and 2 A.M.

Aconite has been suggested in hemoptysis, and its use, when controlled in the foregoing manner, may prove to be very beneficial. It also reduces the force of the heart and slows it. The administration of nauseants (apomorphine, tartar emetic, ipecac, antimony, etc.) for this purpose is hardly to be recommended, although the use of table salt, either a teaspoonful, or in a supersaturated solution with ice, is a favorite remedy of many patients.

Atropine in doses of gr. $\frac{1}{120}$ (0.0005 gm.) may be given hypodermically every four hours for a time in severe hemoptysis, or, if well borne previously, gr. $\frac{1}{60}$ (0.001 gm.). Weismayr, who believes it reduces the blood pressure, has given it in doses of gr. $\frac{1}{25}$ (0.0025 gm.). Digitalis raises the blood pressure, but shows the heart and steadies it, and in some cases of prolonged or slight hemoptysis, due probably to congestion, seems to be of special value.

The coagulation time of the blood in hemoptoic cases has not been determined so far as can be learned. Calcium salts have been suggested to increase the coagulability. In many hands they have not given any striking results. The lactate in doses of gr. xv to xx (1.0 to 1.3 gm.) should be given in water three times a day or gr. xxx (2 gm.) administered night and morning for three days. Strontium or magnesium lactate 15 to 30 grains (1 to 2 gm.) may replace the calcium salt. Lime-water, added to the milk, has also been employed for the same purpose. If the coagulation time of the blood cannot be followed the calcium should be given three days and omitted two (Boggs). Acids, such as lemonade, should be avoided, for they prolong coagulation.

Turpentine has been warmly recommended and is said to increase the coagulability of the blood as well as to possess astringent and vascular depressant (?) qualities. Dilute sulphuric acid is said to aid coagulation.

Limiting the movement of the chest has been advocated. Strapping the affected side and the use of sand-bags has been suggested, but it is by no means easy in all cases to detect the origin of the blood.

While the value of rest cannot be overexaggerated in the treatment, *exercise* is not always highly injurious. Several observers have recently adopted, and with excellent results when prolonged rest was of no

avail, carefully graded exercises for patients with slight, but persistent, hemopytsis.

If the sputum be merely blood-tinged, or slightly streaked, and if hemoptysis has never occurred before, the patient, if in an incipient stage, should be cautioned against any exertion for a few days. Such an occurrence, however, in an advanced stage demands rest in bed.

Narcotics.—Morphine, and less effectually codeine, help to produce absolute rest, quiet the circulation, check the cough, and so help in the formation and protection of the thrombus, but their use is not unattended with danger. This very quieting effect may result in producing areas of bronchopneumonia due to retained blood and secretions. For patients laboring under excitement, with a bounding pulse that cannot be quieted by other means; for those with great fluctuations in the blood pressure, and particularly in those cases in which hemoptysis recurs during the night or early morning hours, morphine is invaluable. When used it should be given hypodermically in doses of gr. $\frac{1}{8}$ (0.008 gm.) and in a few instances for one or two doses of gr. $\frac{1}{4}$ (0.016 gm.). It may occasionally be necessary to give it every four hours, but as a routine, codeine, gr. $\frac{1}{4}$ (0.016 gm.), should always be preferred unless it excites the patient. Inhalation of chloroform has been recommended.

The use of astringents cannot be upheld. The question of stimulation after hemoptysis frequently arises. Digitalis, strychnine, camphor (oxyphor), and alcohol have been used. The latter should be sparingly given. A low blood pressure, it must not be overlooked, is conducive to thrombosis. It is rare that any treatment for anemia is required. There is some prejudice against iron, which should, however, be freely used if necessary.

Complications.—The treatment of many complications must be modified, and it is unwise to aspirate a pleuritic effusion if the sputum be blood-tinged. In one patient suffering from hemoptysis appendectomy was successfully performed.

Surgical Treatment.—The excision of one or more ribs over a cavity, when persistent hemoptysis is present, has given little permanent relief, but the production of artificial pneumothorax should be tried in every case of prolonged or repeated severe hemoptysis.

Prophylaxis.—Patients who have had repeated hemoptyses should exercise with great caution, and all violent respiratory movements must be forbidden. Women who have premenstrual hemoptysis should remain in bed during this period.

Night-sweats.—The hygiene of the skin should receive special attention. The patient should wear woollen night-robes and in cool weather sleep between blankets, but should carefully avoid too much covering, especially over the feet.

When sweats occur in weak patients, nourishment should be frequently administered, especially at night whenever the patient is awake, and in some instances he should be aroused and food given two hours before the expected sweat. Two or three drams of brandy in the milk given at bedtime is often better than plain milk. Sponging at bedtime with an ounce of toilet or table vinegar, or of eau de cologne, in a pint of

water, or even with pure vingear, is very effective in many cases. Combined with equal parts of alcohol (95 per cent.), the commercial formalin (40 per cent.) has been painted on the skin every day. Its application should never be intrusted to the patient. Various combinations of formalin in powders have given some relief when dusted on the skin. Salicylic acid has been employed successfully as a powder (salicylic acid, 3 parts; starch, 10 parts; talcum, 87 parts).

A cold compress to the entire chest worn all night, or an ice-bag applied to the abdomen for several hours in the evening, lessens the sweats in many patients who get relief in no other way.

Medicinal treatment should be resorted to only when all other measures have failed. Camphoric acid, gr. xij (0.8 gm.) at bedtime, should be first tried and the cough treated if necessary. Zinc oxide, gr. iij to v (0.2 to 0.35 gm.) at bedtime; aromatic sulphuric acid, ʒss (2 cc.) at bedtime, may both be tried; but in many cases it is wise to use atropine, either alone or in combination with a little morphine and a mineral acid.

Dyspnœa.—When complications are excluded there remain many distressing cases of dyspnœa, such as those caused by rapid extension of the disease and by mechanical factors. Patients with advancing fibrosis and small pulmonary capacity should be told of their limitations, which they should not exceed. If due to weakness or to great difficulty in raising the sputum, stimulants and expectorants may be used. Oxyphor (an alcoholic solution of oxycamphor), in does of 10 drops on a little sugar every three or four hours, often affords the greatest relief. There are, however, patients to whom these measures afford no relief, for whom heroin soon loses its effect, but who are markedly relieved by the use of morphine in very small quantities. It should be reserved for patients in the very last stages or for those acutely ill. The indications for the use of oxygen and of morphine are very similar.

Tachycardia.—Rest in bed or on a reclining chair has a marked effect, and should be insisted upon in all early cases when the pulse is persistently above 100. Severe exercise, excitement, coffee, tobacco, alcohol, and all indigestible food should be avoided. Carbohydrates and in some cases all food may have to be limited. If cardiac distress or palpitation occurs, an ice-bag over the heart is often sufficient. Bromides, valerian, chloroform, and menthol may be of service, but digitalis and caffeine are of little value.

Pain.—*Pleuritic.*—The treatment consists chiefly of immobilizing the side and in counter-irritation. Acute pleurisy demands rest in bed, and the cough, when severe, should be checked. In acute attacks the side should be strapped with zinc oxide adhesive plaster. The straps (two or three in number) may be applied about the thorax during full expiration, reaching two or three inches beyond the midlines, front and back, or one or two straps, if the pleurisy is in the axilla, may extend entirely around the thorax. A canvas jacket made with stays and laces with straps reaching over the shoulders affords great relief to some patients. Corsets help some women.

External Applications.—Heat or cold may be applied, the latter best in the form of an ice-bag. Liniments are often useful and mustard poultices, mustard leaves or papers, or painting with the tincture of iodine, are all of value. It is wise to apply the mustard or the iodine to a number of small areas of skin about the size of a postage stamp, leaving fully as large an area between for future applications if necessary. Ointments containing menthol, belladonna, and opium may be rubbed in. The cautery, lightly applied, is far superior to most applications. A blister under the clavicle may aid when the pleurisy is in this region. Cloths kept moist in a saturated solution of magnesium sulphate and applied for some hours may be very helpful (Tucker).

Medicinal.—Sodium salicylate up to ʒiss (6 gm.) per diem if necessary, followed by smaller doses, gr. viiss (0.5 gm.) with or without potassium iodide, is held by some to be almost specific. Aspirin, acetanilide, and phenacetin are helpful, and, finally, in a very few cases, morphine must be used.

Hyperesthesia.—Massage, local hydrotherapy, electricity; belladonna and opium plasters; iodine locally; ointments of veratrine, of chloral, cocaine, and menthol; and chloroform in oil may be used. Often the condition requires no treatment save a word of encouragement.

Treatment of Complications.—This interferes little in many cases with the general treatment. As a rule it is easy to decide whether or not, for the time being, the outdoor life must be abandoned; if any doubt arises it is wise to treat, first, the pulmonary lesion. The patient if confined to bed should be placed in a room which opens on a porch upon which the bed may be moved.

Nose.—Obstructions should be removed as soon as the patient's condition warrants it. Tuberculous ulcers should be treated by scraping, followed by lactic or chromic acid.

Influenza, Coryza, Bronchitis.—The patient with influenza should be isolated and repeated attacks would suggest the advisability of the isolation of the organism and the use of vaccines. If fever be present, the patient should be in bed. In catarrhal conditions of the upper air passages the patient should remain indoors until the acute stage is over. For the intercurrent attacks of coryza, leading often to laryngitis, tracheitis, and bronchitis, a full hot bath (110° to 115°) at night, followed by a cold spray, the use of salol, of a mixture of liquor ammonii acetatis, ʒij (8 cc.); paregoric, gtt. x (0.6 cc.); sweet spirit of nitre, ♏xv (1 cc.); and camphor-water, q. s. ad ʒj (30 cc.), every four hours, may abort the attack. For the succeeding bronchitis after the acute stage is passed, nothing is better than creosotal (♏v) after meals. The cold chest bath should be practised each morning throughout the attack. A drop of the tincture of aconite every hour for a few doses often aborts a cold.

Pleuritic Effusion.—Delafield has advocated paracentesis as soon as effusion is diagnosed. Sweating, purging, and restriction of fluids may be tried in chronic cases. Careful respiratory exercises should be begun as soon as the fever abates.

Empyema.—When due to other organisms the chest should be incised, but when tubercle bacilli occur alone two needles should be introduced, and the chest thoroughly irrigated with 0.6 per cent. solution of sodium chloride. A small quantity of iodoform may be finally injected.

Pneumothorax.—This admits of little choice at first; later the treatment may be conservative or radical. Absolute rest in the reclining position, application of straps or hot flannels, morphine (to be administered with great caution) for the pain; the diffusible stimulants, ether and brandy, aromatic spirit of ammonia, digitalis or strophanthus if collapse set in, and amyl nitrite, should be tried when the symptoms are urgent. It may be necessary to relieve the tension of the air at once, and, if the opening be valvular, West's method of leaving a needle *in situ*, from which a rubber tube runs into a vessel of sterile water, may be employed advantageously. Mild purgation should be used after the first day. Absolute rest is most important. When effusion takes place quickly it seems undoubtedly wise to refrain from aspiration for several days, and then it should be removed with as little suction as possible. The siphonage method should be tried. The use of two needles and washing out the pleura with boric-acid solution Fowler finds helpful in many cases. Thoracotomy and even thoracoplasty may have to be resorted to, especially when pyopneumothorax supervenes. As this usually results fatally, and as many hold that radical operative interference hastens the end, it should be carefully considered. West strongly advocates incision in such cases and reports good results.

Secondary Infections.—The results of antistreptococcic serum up to this time have not been very satisfactory and the treatment is not entirely devoid of danger. A vaccine, made from organisms from washed sputum, to which the patient's opsonic index is low, has been found of value, especially in chronic stages with abundant sputum. Creosote and its derivatives are very effective in some cases. Inhalation of vapor from carbolic acid ($2\frac{1}{2}$ per cent. in water) for fifteen minutes night and morning, as well as of creosote, have all been recommended.

Anemia.—In the majority of cases the hygienic-dietetic treatment is all that is required. Nothing, however, is more efficacious than Blaud's mass with gr. $\frac{1}{6}$ (0.01 gm.) of the extract of nux vomica after meals.

Digestive Disturbance.—Every means should be used to determine the cause, which in not a few instances is overfeeding. Lavage need not be feared except in case of a recent hemoptysis, and a test meal should always be given in prolonged disturbances.

Prophylaxis.—Many patients have to be taught how to expectorate. Sputum when swallowed may cause a simple diarrhœa, almost impossible to control, or tuberculous enteritis.

Flatulence.—The treatment of this symptom should be at first dietetic. All fluids at meals should be avoided unless at the very end. Milk may have to be modified or even given up for a time and the diet restricted largely or wholly to albuminous food. Effervescing waters should be avoided.

Dilatation of the Stomach.—The fluids should be limited, the abdomen may be supported with straps, the patient should lie on the right side

at intervals for one or two hours after meals, and finally recourse may be had to daily or semiweekly lavage.

Vomiting and Nausea.—It is wise for a few days to put the patient in bed, restrict the diet to peptonized milk, hot or iced, or feed per rectum. This together with lavage is often sufficient. If symptoms of dyspepsia have been noted, the diet may have been too bulky, or fermentation and decomposition may have occurred, with subsequent irritation. Gastric sedatives are indicated. For nausea, restriction of food, drop doses of the tincture of nux vomica every fifteen minutes, and other remedies used for vomiting may be given.

Anorexia.—Rest out-of-doors is sufficient to restore a lost appetite in many patients who have been at work. If too prolonged rest has been followed, carefully regulated exercise is often helpful. All lunches between meals should be stopped and if the anorexia is pronounced the patient should be put to bed and fed on liquids. The most important factor is often a complete change of surroundings and of table. If fever be the cause, antipyretics may be used advantageously, especially pyramidon. Bitter tonics, a little Vichy, or a drop or two of creosote in water, or a little whisky or wine with the meal often aid. The false appetite, a desire for food until the first few mouthfuls are taken, when all appetite is lost and nausea may appear, may be benefited by nux vomica or dilute hydrocyanic acid before meals.

Constipation.—Every other means should be tried before drugs. The quantity of water, especially between meals, must be sufficient, and the patient should eat freely of fresh and preserved fruit. Massage of the abdomen relieves some. Glycerin suppositories and enemas of olive oil at bedtime may be effective. The large amount of food consumed makes the condition of the bowels of great importance, and an occasional dose of castor oil, of calomel and a saline, are in some cases a necessity and aid most patients.

Intestinal Tuberculosis.—The treatment of this is usually unsatisfactory. In all severe cases the patient should be kept at rest and in bed for a time at least. All fruits, fruit juices, salads, most vegetables, sugar and other sweets should be avoided. Beef juice, egg-yolks, and certain prepared foods may increase the diarrhœa. If severe, the diet should be much restricted and limited to boiled milk and albumins or rice-water for a few days. Fluids should be restricted and cold drinks avoided. Tea, cocoa, and bean coffee may be taken in moderate quantities. Lime-water or cognac may be added to the milk or it may be peptonized or given as koumiss.

Saline irrigations are useful and a few drops of laudanum may be added. Mueller warmly advocates an injection of ʒj to ij (4 to 8 gm.) of bismuth subnitrate in 250 to 300 cc. of warm water, to be retained for ten to fifteen minutes, preceded by a cleansing enema. A few drops of laudanum may be added when necessary. An abdominal band of flannel or silk should be worn night and day. Local applications to the abdomen may give great relief, and turpentine stupes, repeatedly applied, often relieve the severe abdominal pain. An ice- or hot-water bag may in some instances be helpful. A limited resection, especially

ileocecal, or lateral anastomosis may afford much and in a few cases permanent relief if the patient can stand the operation. The usual drugs may be employed. Sooner or later the majority have to resort to the use of opium by enema or suppository.

Peri-anal Abscess and Fistula-in-ano.—Warm, moist applications should be applied until pus forms, when, under a local anesthetic, the abscess should be incised. In a few instances the abscess heals, but usually a fistula results, which, when the patient's condition warrants a general anesthetic, and when well defined by scar tissue, may be excised. Fistulæ can exist for years and exert little or no discernible influence upon the general health if carefully and frequently cleansed. The injection of mercurial ointment into, or of tuberculin about, them has in some cases resulted in healing.

Arthritis.—Patients with pulmonary tuberculosis and arthritis do better in warm, equable climates. The salicylates, aspirin and salol, are usually well borne, and oil of wintergreen may be applied.

Syphilis.—This need in no way interfere with the routine treatment. Potassium iodide, mercury, and salvarsan are well borne.

Menstrual Disturbances.—Amenorrhœa is frequent, and, unless accompanied by some discomfort, requires no treatment. Many patients suffer considerably at this time, and rest in bed should be advised.

Pregnancy.—Conception should be avoided in all cases when the patient has not been well for at least two years. The dangers of repeated pregnancies should be carefully explained. When pregnancy occurs, abortion should be considered if the pregnancy is in the first three or four months. Tuberculous laryngitis and nausea and vomiting in the early stages are always positive indications for abortion, which should be performed by the quickest and least laborious method. At term labor should be allowed to proceed to the beginning of the second stage, when chloroform should be administered and forceps applied. The mother should not nurse the infant, but a wet nurse may be employed or modified milk be used. It is often well to institute a short course of treatment after delivery in patients whose disease has been long cured.

Insomnia.—The patient should not sleep during the day. The room should be dark, well ventilated, not too cool (40° to 50°), and the bed warm. Some patients sleep much better out-of-doors. A wet pack to the abdomen, legs, calves, or feet, or even a full chest pack may be efficacious. Massage of the back is often helpful. Fever may cause insomnia and the temperature should always be taken at night for a time when insomnia occurs.

Medicinal Treatment.—The "antiseptic treatment," based on the idea that it is possible to destroy the tubercle bacillus *in situ* without harming the tissues, needs only to be mentioned to be dismissed. The view that healthy contiguous parts may be protected in this way has never been proved by clinical experience, either in pulmonary or localized surgical forms of tuberculosis. No medicinal substance has been found to neutralize the tuberculous poison.

Creosote and its Derivatives.—These have no action whatever upon the tuberculous process, but in some cases seem to act almost as a specific

upon the accompanying bronchorrhœa and intercurrent attacks of simple bronchitis. Their action is no doubt due in part to their effect upon the secondary organisms and in part to a stimulating effect upon the bronchial mucous membrane during their excretion through it. For this effect small doses only are necessary in most patients, and Sommerbrodt's dictum that the larger the daily dose the better the results cannot be upheld. Drop doses of creosote act in some patients as an excellent tonic for a poorly secreting stomach, an explanation of the benefit of combining it in these quantities with cod-liver oil. Among the contraindications are a persistent taste of creosote, gastric irritation, and nephritis. The patient should always be warned to stop it or any medicine if the slightest digestive disturbances occur. Only pure beechwood creosote should be used.

Arsenic.—This has been thought by some to exert a specific action in pulmonary tuberculosis and in some it stimulates nutrition remarkably.

A number of substances which increase the leukocytes have been employed, among which is cinnamic acid. The same effect has been noted in regard to tuberculin, but nucleic acid stands as the best example of this class. Cinnamic acid is said to prevent or replace caseous matter by vascular connective tissue, forming true cicatrices, to increase the lymph flow, the alexins, and thus to produce healing of tuberculous lesions. It has been administered by ingestion, by inhalation, by subcutaneous injection, but preferably by intravenous or intramuscular (intragluteal) injection.

Various salts of calcium (carbonate, bicarbonate, phosphate, iodide) have been given by mouth or hypodermically, alone or in combination with creosote, tuberculin, etc. The calcium salts are said to be deposited at the foci of the inflammation and afford a mechanical stimulus which starts and aids the process of repair (Michelozzi). On account of the demineralization in pulmonary tuberculosis, lime-salts are of value, but exert no specific action.

Strychnine, gr. $\frac{1}{30}$ (0.002 gm.), is of value. It acts advantageously upon lowered blood tension, weakened heart, jaded appetite, and neurasthenia.

Alcohol.—This may be said to be a dangerous food and a symptomatic drug of considerable potential danger, but of value in some cases of pulmonary tuberculosis. In a few patients a cocktail or a tablespoonful of whisky taken with the first part of the meal may aid a flagging appetite or weak digestion. One glass of stout, of bitter ale, or of a good wine may do the same. A small amount of brandy or whisky in milk or sherry with egg is permissible if it enables patients to take these foods who otherwise could not. One glass of beer or ale at bedtime or a little whisky may relieve insomnia, but these are dangerous remedies. A few patients with slowly progressing, chronic disease unquestionably prolong their existence by a judicious, although rather free, use of spirits.

Specific Treatment.—Tuberculin.—Many observers believe that the majority of tuberculins used clinically are of equal value, but heat above 60° C. and chemical manipulation may injure bacterial vaccines. For

this reason it would seem wisest to select those tuberculins which have been subjected to the least manipulation.

From theoretical considerations it would seem that the most rational tuberculins named in the order of the dates of their discovery are B. F., T. R.,[1] B. E., and a mixture of B. F. and B. E. B. F. contains the products of the tubercle bacilli disintegrating during the growth of the culture, as well as any unchanged products of the tubercle bacillus given off in its growth, and, while less toxic than O. T. and possibly to be preferred for this reason for febrile patients, it may possess some immunizing properties destroyed by the prolonged heating to which O. T. is subjected. B. E. possesses all the immunizing substances in the tubercle bacillus and is subjected to heat of only 60° C. An emulsion of B. E. and B. F. would, therefore, seem to combine whatever immunizing properties exist in either the tubercle bacillus or the culture fluid. K. Spengler strongly advocates B. F. of bovine origin (his P. T. O.), believing it causes few reactions and better immunity in infections with the human strain of tubercle bacillus. B. E. in large doses may cause sterile abscesses. B. E. and T. R. cause more local reaction at the site of inoculation, but apparently little more frequent, though less readily controlled, general reactions than O. T. or B. F.

Many other tuberculins have been used and possibly are of equal value, viz., O. T., watery extract, Beraneck's tuberculin, and tuberculol. Apparently of less value may be mentioned Trudeau's and Hunter's modification B., tuberculocidin, antiphthisine, purified tuberculin, oxytuberculin, tuberculoplasmin, and tuberculin from fowl and fish tubercle bacilli.

Tuberculin should be administered to patients who are afebrile and in a state of good nutrition. Many patients who have long followed the hygienic-dietetic treatment seem to reach a state where no further improvement occurs. They no longer have fever, the bodily weight is above normal, but cough, expectoration, and physical signs persist, and tubercle bacilli are still to be found in the sputum. These patients should always be subjected to tuberculin treatment in hope that chronicity may be avoided. It is also indicated in early closed pulmonary tuberculosis, and many have recommended its use in members of "phthisical families," who as yet present no evidence of the disease. Children do well under its use.

Patients with persistent slight pyrexia, which rest does not affect, may lose it under tuberculin. If, however, the temperature reaches 101° it is wise to begin with doses smaller than usual, to increase with the greatest caution, and to abandon the treatment if any stubborn intolerance is manifested. In such patients too much must not be expected from tuberculin. It is rarely wise to administer tuberculin to patients whose minimum temperature does not fall below 99° every day. In patients who have had frequent or repeated hemoptysis

[1] The following abbreviations for the various tuberculins are used throughout this article: O. T., Koch's original tuberculin; T. R., tuberculin residuum; B. E., bacillen emulsion; B. F., Deny's bouillon filtré. For full discussion see Hamman and Wolman: Tuberculin in Diagnosis and Treatment, 1912.

great care should be used. In pulmonary tuberculosis with secondary infections, the tuberculin treatment and vaccination against secondary organisms may go hand in hand.

As contra-indications to tuberculin treatment may be mentioned: rapid loss of flesh, malnutrition (so frequent in late stages), meningitis, acute miliary tuberculosis, nephritis (non-tuberculous), epilepsy, pronounced nervousness, and a persistent pulse-rate above 100. Excellent results have been obtained in ambulant patients in incipient stages.

The advice to be given patients inquiring in regard to tuberculin treatment is of great importance. It should be frankly explained to them that tuberculin carefully given can produce no harm, but that it may be to them of little or no immediately apparent value.

The administration of tuberculin by ingestion, inhalation, inunction, or intratracheal or intravenous injection is not recommended.

Dosage and Interval.—In the proper selection of the dose and of the interval between doses lies the key to the successful treatment. Tuberculin should be looked upon as a most powerful poison, capable of producing irreparable harm in ignorant or careless hands. The slightest departure from the ordinary course of events should be thoughtfully considered. The tolerance to the tuberculous toxin varies greatly (from 1 to 10,000, Sahli) and apparently is independent of sex, of amount of pulmonary involvement, and of general physique.

The beginning dose should always be far below that expected to excite reaction. In febrile patients and in those who have been subjected to the tuberculin test it should be smaller than in others. In B. E., Koch's beginning dose of 0.0000025 gm.[1] should be reduced to 0.000001 gm. for afebrile and to 0.0000001 for febrile patients. This is also the dose of T. R. For B. F. or O. T., the usual beginning dose may be 0.0000005 or 0.000001 cc., though in a few, especially if febrile, it may be 0.0000001 or 0.00000001 cc.

The increase of the dose depends entirely upon the individual. The usual method is to make each solution ten times the strength of the preceding and to increase the dose as follows: 0.10, 0.12, 0.15, 0.18, 0.22, 0.26, 0.32, 0.38, 0.47, 0.56, 0.68, 0.86, 1.00 cc. or 0.10 of the next solution. In many afebrile cases alternate doses may be omitted. This will prevent the cumulative action or the hypersensibility produced by too large doses and is especially applicable in febrile patients.

The greatest care in increase should be exercised in giving tenths of a milligram of O. T. or hundredths or tenths of a milligram of B. E. or B. F., as reaction most frequently occur during these doses. Once past this point without reactions, they are much less likely to occur. A large percentage (43) of patients first reacted when taking some tenths of a milligram of B. E.

The effect of small, often-repeated doses of the various tuberculins has not been sufficiently studied, although the work of Loewenstein and his assistants would suggest the danger of acquired intolerance by

[1] B. E. and T. R.: Doses always given in solid substance of tubercle bacilli in suspension.

such a method. Wright has not noted any such tolerance with very small doses. The work of Hastings and of Kinghorn shows that, with increasing the large doses of O. T. and B. F., the negative phase of Wright does not occur, and, when it occurs, need not be considered.

It is best to administer tuberculin twice a week from the beginning, for in some cases a retarded reaction occurs. When larger doses are reached or greater susceptibility is manifested, intervals of one week or longer are often advisable. If an intermission of several weeks is required it is wise to decrease somewhat the following dose:

The maximum dose to be attained in any patient varies with the individual. The relation of the size of the final dose to the benefit derived from the treatment has not been worked out. The extent of the pulmonary lesion or of the change in the physical signs bears no necessary relation to the tolerance, although with advancing disease or the onset of complications the tolerance is often decreased. In B. E. 5 mg. (solid substance) should not be exceeded, while in O. T. and B. F. 1 cc. is the usual maximum dose. The maximum dose is often repeated several times.

Tuberculin administered according to these directions rarely excites any reaction until the larger doses are reached, and even then O. T. and B. F. rarely cause reaction. When a patient has once been found to be tolerant of tuberculin the increase may be more rapid. This tolerance may be determined more rapidly by injecting 0.000000001 cc. intradermically and increasing the dose ten-fold until signs of marked reaction appear. A slightly reduced dose should then be given subcutaneously and tolerance to large doses may be more quickly obtained. The Bacillen emulsion (B. E.) of Koch (a $\frac{1}{2}$ per cent. emulsion of tubercle bacilli) may be measured similarly as B. F., *i. e.*, by ignoring the solid contents and by taking into account only the liquid contents. The beginning dose (0.000001 solid substance) is contained in 0.0002 cc. This can also be carried out with T. R. The schema of increase for B. F. may then be followed. In any case, no matter how tolerant the patient is, the first course should be extended over five months. This can be readily done by lengthening the interval between the doses or by increasing the dose more slowly.

W. C. White gives a cutaneous test with a carefully measured quantity of diluted tuberculin in an attempt to determine what subcutaneous dose will just fall short of producing a general reaction. He then repeats this dose every two weeks.

If at any time during the course of treatment another "brew" or a different lot of tuberculin be used, the dose should be reduced.

All physicians who are not thoroughly familiar with the technique should give it *most carefully* and, one might almost add, fearfully. The slowest increase should be sufficient for them, and the slightest departure from the usual course on the part of the patient should be seriously considered and the dose increased or decreased accordingly.

Duration of Treatment.—No patient should be given tuberculin who cannot follow this treatment for at least five months, although shorter courses seem to be of some benefit. In the more advanced stages a

longer duration is required. In most patients the focus of disease is rarely in one stage of development, and hence the need for long-continued treatment. The second and following courses of tuberculin may be given at home by the patient's physician.

The hygienic-dietetic treatment should be faithfully followed throughout the treatment. Exercise should be curtailed on the day of injection, and on the following days it is wise, especially if there be any tendency toward reaction, to keep the patient at rest in his reclining chair. The temperature should be taken before rising, and at 4 and 8 P.M., also at any time of the day if the patient feel indisposed; in addition the weight and any unusual symptoms should be noted. If the temperature reaches 100° for more than two hours, rest in bed should be enforced until the temperature falls to normal if the reaction be slight, or for several days in cases of a severe reaction. The headache during reaction or pain at the site of injection is best treated with an ice-bag or cold applications. The majority of patients have some manifestations of a reaction at different times during the treatment, but it is not rare, with carefully adjusted doses, for patients to escape reaction. Failure to observe the slighter symptoms of intolerance is the explanation of many failures with tuberculin. It should never be given when a patient is suffering from a coryza, acute bronchitis, gastric disorder, and fatigue or, in fact, is feeling "out of sorts" from any cause.

In most patients there comes a period of increased susceptibility when an increase in dose, which before caused no disturbance, results in a violent reaction. The same dose should be repeated many times if necessary, or the interval lengthened for a time. In most patients who have been subjected to the tuberculin test it is accentuated. By great care it can practically always be readily overcome.

At the site of injection slight redness, swelling, and soreness are not uncommon, occurring most frequently after B. E., less after O T., and less still after B. F. Large doses of B. E. leave indurated areas, which should always be avoided on future injections, for otherwise sterile abscesses may arise. The reaction at the site of inoculation depends partly upon the volume of the dose, less upon the concentration, and chiefly upon the site, occurring least often in the subscapular region. If the symptoms are pronounced the same dose should be repeated. In all instances of a slight rise of temperature no tuberculin should be administered until the temperature has been normal or at the same level as before for two days. After a rise of temperature of 0.5° to 1° without other symptoms, the same dose at the usual interval should be given. If the temperature rise above 99.6° (in a patient with normal temperature) without other symptoms, the dose before the last should be given. With the same rise of temperature accompanied with symptoms, the next dose should be reduced to one-half to one-fifth of the last dose, or even less. When the temperature reaches 100.4° or over (rarely unaccompanied by symptoms) the dose should be similarly reduced and not given for at least a week. Tuberculin should never be given again until all symptoms produced by the last dose have completely subsided. If the symptoms were slight, an intermission of one

normal day is sufficient; but if pronounced, at least three or four such days should intervene before the next dose.

The pulse is often quickened and at times the patient may complain of tachycardia. Dyspnœa or a sense of oppression occurs in a number of cases, resulting from overdosage. The sputum, blood, and urine are of little aid in foretelling reaction or determining the dose. Rise of temperature is often absent when headache, pain in back or limbs, malaise, fatigue, loss of appetite, or weakness occurs.

If these symptoms occur separately and are only slightly pronounced, the same dose should be repeated. If any one is severe or if several are present the dose should be reduced. With severe reactions various rashes may occur and enlargement of the lymph glands (axillary). In this case the following dose should then be much reduced and given at an interval of at least a week.

A continuous, even if slight, loss of weight, when below the normal, means cessation of treatment for a time at least. Care about dosage should be exercised if stimulation occur, for this is often succeeded by depression.

Symptoms of local pulmonary reaction are not often marked with carefully adjusted doses. The cough and expectoration not infrequently increase for a time and, unless severe, need not cause a reduction of the dose, although it may be wise to repeat the same dose several times. It is unwise to give tuberculin to a patient with acute pleuritic pain. No tuberculin should be given for two weeks after a hemoptysis of 5 to 10 cc. or more, and it is usually wise to reduce the succeeding dose.

The relation of the increase of physical signs to the dosage has not been fully worked out. Marked changes do not usually occur until large doses are reached, and even then are far from constant. It is a wise proceeding to repeat the same dose until marked evidence of increase of physical signs is no longer present. An increase of dose, however, during this time seems to do no harm.

This method of using tuberculin is based solely upon clinical experience, and the effect of any one dose cannot be accurately estimated. So far no practical method has been discovered by which the effect of each dose can be followed and the succeeding dose properly estimated. Many reactions can, however, be avoided by careful clinical observation. The patients should be taught to record accurately any symptoms, however slight. Even the most pronounced neurasthenic patients, if given tuberculin, betray no increased nervousness on account of keeping such a record, and, at least in the writer's experience, often less.

The Effect of Repeated Tuberculin Injections.—Tuberculin in sufficient doses causes a congestion of the tuberculous foci, long thought necessary for healing, although recently doubt has been thrown upon it by the work of Wright. The local (organ) reactions in patients with mixed infection following large doses may result in great harm. Large doses of tuberculin are said to cause increased fibrosis about the tuberculous foci and elsewhere.

Injection of tuberculin causes the formation in the serum of anti-tuberculin bodies; B. E. causes marked increase of the agglutinins for

tubercle bacilli. Arneth, through a study of the nuclei of the polymorphonuclear leukocytes, concluded that the blood picture becomes more nearly normal. Lupton and Brown found a slight increase in the leukocytes, which only in the rarest instances, however, reached 10,000 per cmm. The sputum is increased at first and may be more purulent. Later it often decreases or ceases. Tubercle bacilli disappear more frequently from the sputum in treated patients.

The writer's notice has repeatedly been called to the fact that many patients, treated with tuberculin, deserving apparently a poor prognosis, have enjoyed freedom from febrile attacks and escaped complications, apparently more often than the non-treated patients.

The "Opsonic" Method.—In their work Wright and his followers have employed tuberculin T. R. or an emulsion of tubercle bacilli heated on three successive days to 60° C. only. The dose employed has ranged between $\frac{1}{1000}$ and $\frac{1}{500}$ mg. of the solid substance. They have not found it necessary to increase the dose, and it is timed by following the opsonic-index curve. The injection is usually made when, after a rise, the curve begins to fall. Their results are less successful in pulmonary than in other forms of tuberculosis.

Treatment with Bacteria.—Many living bacteria have been used in the treatment of tuberculosis. Human tubercle bacilli have been employed with marked success in cattle. The attenuated forms markedly prolong the life of guinea-pigs. However, the time may yet come when tubercle bacilli attenuated by some means can be used in man, although some now recommend and practise this method.

Inoculations of acid-fast bacilli have little effect other than causing agglutination of tubercle bacilli. Many other bacteria have been used, but the results are unsatisfactory.

Vaccination with the secondary organisms has been used by Denys and Wright. The serous exudate of blisters has been used as a specific by Mangant, and others (Flick, etc.) have advocated the production of blisters, protecting them carefully in order to allow the contents to be reabsorbed.

Serotherapy and Organotherapy.—Antitoxic serums have met with little success and the danger of anaphylaxis, though slight, is real. The injection of normal serums has yielded no benefit.

The extracts of the lymphatic glands or the powdered glands have been given, but without marked success.

Hydrotherapy.—This helps in withstanding cold (hardening process), strengthens the heart, slows the pulse, increases the vasomotor tone of the cutaneous bloodvessels (and so raises the blood pressure), often aids the appetite and causes deeper breaths to be taken. Its effect upon the nutrition and secretion of the skin is marked. Great freedom from colds is enjoyed by many patients who follow these methods—a most important point. Every patient should take daily, preferably on arising, a cold bath. After drying himself, he should experience a glow. Should this not occur or if heart disease, aneurism, or marked arteriosclerosis be present, it is wise to abandon any vigorous hydropathic measures.

For patients who fail to react and for all patients susceptible to cold, it is wise at the beginning to insist upon a few simple measures. The bath should always be taken in a warm room (never below 55°). All cleansing should be done with warm water (100°), and the cold (40° to 60°) should be applied with a sponge to the neck, chest (front and back), and arms as quickly as possible (about one or two minutes), and immediately dried. It may be necessary to begin the sponging with tepid water or to begin with sponging one arm, then on the following day both arms, and so on until the body to the waist has been sponged. Alcohol rubs may have to be substituted for a time.

For more vigorous patients, especially those long accustomed to it, the instantaneous cold plunge (50° to 70°) may be permitted. Others prefer a cold shower or full cold sponge, standing meanwhile in warm water. For many patients, however, these are not advisable, especially in winter, unless the water is slightly heated. In some patients nervousness is increased by too cold baths. Twice each week every patient should take a warm (100° to 105°) cleansing bath, using soap freely.

Hydrotherapeutic measures directed against the fever have helped little in pulmonary tuberculosis. Every patient with fever and confined strictly to bed should be given each night a brine bath (sea-salt ℥ss in water Oij), the temperature of which should be gradually lowered, but never so low that a reaction fails to follow. An alcohol rub may be given afterward.

The "cross-binder" worn during the night may be of help in severe cough with tenacious sputum, for pain in the chest (pleurisy, etc.), for catarrhal conditions of the upper air passages, and for insomnia.

Electricity and Light.—Static electricity, the *x*-ray, and high-frequency currents are of little value.

Surgical Treatment.[1]—The early excision of the tuberculous focus has been frequently discussed and several times attempted, once or twice successfully, but cannot be recommended.

The early calcification of the first costal cartilage, resulting in lessened movement and narrowed apical aperture, led to the suggestion that in early stages an artificial joint be produced by cutting through the first costal cartilage. It has met with little favor. Numerous observers have advocated that the diseased lung should be put at rest, by strapping the chest, by the injection of air, simple or carbolized, filtered or unfiltered, or of nitrogen gas. The surgical treatment of tuberculous cavities has produced few favorable results. The excision of one or several ribs over a tuberculous cavity or of many ribs to produce collapse of the lung has been advocated for healing and for relief of symptoms. Except in gangrene it is doubtful if pneumotomy is ever of much benefit.

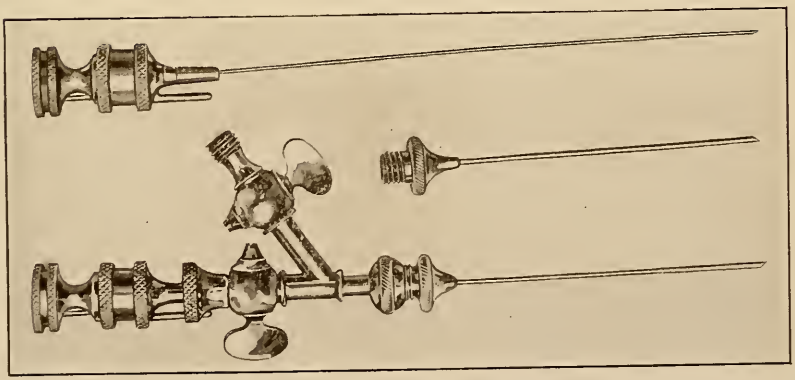
Artificial Pneumothorax.—This adds another to the effective means of treatment of progressive pulmonary tuberculosis. The object of the treatment is to cause complete collapse of the most affected lung. This prevents movement of and entrance of air into the lung, as well as any oxygenation so that all blood in the lung, except from the bronchial

[1] See Garré and Quincke: *Lugenchirurgie*, 1912.

PLATE III

FIG. 1

FIG. 2



Simple Apparatus for Injection of Nitrogen into Pleural Cavity.

Long manometric scale (—40 to +40 cm. H_2O). Floyd-Robinson needle with detachable shaft. Two sizes.

artery, is venous. It reduces the blood content from one-third to one-half the normal and slows the lymph stream. This helps in the encapsulation of the foci, increases the fibrous tissue in the walls of the vessels, bronchi, and septa, but apparently does not affect the healthy part of the lung or prevent its expansion and functioning after months of treatment. The aspiratory action of the thorax is interfered with and less blood supplied to the right side of the heart, in which practically no change occurs. In many cases slight lesions in the breathing lung seem to improve unless too great pressure is maintained in the pneumothorax or the mediastinum is displaced.

The ultimate results are as yet difficult to determine. Too few patients ever have complete collapse, but even for these the treatment is at least temporarily helpful. When the patients are carefully selected about one-half are more or less permanently benefited. But many pitfalls lie along their paths and slight intercurrent pulmonary affections may prove disastrous. However, the treatment is worthy of trial in all suitable cases which have failed to improve under other methods and the permanency of the treatment may be looked upon as assured.

Method.—The apparatus can be extremely simple, consisting of two large bottles, one filled with gas, the other with a solution of boracic or pyrogallic acid and connected with the first by a siphon (glass and rubber tubing). A water manometer, filled with boracic acid, colored with methylene blue, registering from +40 to −40 cm., is connected by a "Y" with the tube leading to the gas bottle and to the needle. A few pinch cocks and possibly a box in which to transport it completes the apparatus (Plate III, Fig. 1). The needle is shown in Plate III, Fig. 2.

The site of injection should be in the lower part of the chest and not too near the heart. When convenient the patient should be so placed that it will be the highest part of the thorax. Areas which possibly overlie adhesions should be avoided.

In nervous patients, it is wise to give morphine gr. $\frac{1}{4}$ (0.016 gm.) one-half hour before the injection. The area about the site should be painted with tincture of iodine and a solution of novocaine and adrenalin ($\frac{1}{3}$ gr. and $\frac{1}{200}$ gr. respectively in about ʒiij or 15 cc. of boiled water) injected first into the skin and then into the muscles and pleura.

The needle is then inserted, and when it is thought to be through the pleura it is connected with the manometer. This is the critical point in the operation. If the needle be in the chest wall the manometer level is stationary, if it touch but not penetrate the parietal pleura a slight variation of 1 or 2 cm. may be obtained; if too deeply inserted, *i. e.*, into the lung, the pressure may vary from +1 to −2 cm. H_2O. If, however, it be in the pleural cavity, the pressure will vary from 0 or −1 to −5, to as low as −15 or −20, depending upon the adhesions present (the more adhesions the higher the pressure). When a good negative pressure (−6 to −10) with a variation of 5 to 10 or more cm. of water is obtained, the gas may be safely allowed to flow in. Only 300 to 500 cc. of gas should be introduced at first, although many inject more. The second injection should be given the second day following the first, and from 300 to 500 or 600 cc. introduced. After

3 or 4 days 600 to 1000 cc. may be injected and from this time weekly, and later even only monthly, injections are required, as the pleura loses its power to absorb the gas. It is wise not to raise the inspiratory pressure above 0 if possible, but when adhesions and only a partial collapse are present, a pressure of +10 to +20 cm. of water may be left in the pleura or better, even higher pressure be employed for a few minutes in order to separate the adhesions if possible.

The danger of injecting the gas into the pulmonary vessels has led some to advocate an "open" method, which consists of laying bare, under local anesthesia, the parietal pleura and introducing a blunt cannula into the pleural sac. This may subject the patient to graver dangers than the "closed" method, which is to be preferred.

Gas.—Filtered air may be used, but, like oxygen, is absorbed too quickly, and nitrogen, which can be obtained in tanks, is to be preferred.

Selection of Cases.—Artificial pneumothorax should be attempted in every case of severe pulmonary tuberculosis in which other treatment has failed and the lesion is practically limited to one side, except when complications elsewhere are so severe that they alone will terminate life. Severe and repeated hemoptyses in the absence of pleuritic adhesions, may be quickly checked. The presence of these adhesions is difficult to determine, but when the intercostal spaces are narrowed and fixed, when movement is limited, the ribs drawn in, or where by radiography the rib contour is indefinite, the intercostal space darkened and narrowed, when Litten's sign is absent, movement of the lower pulmony border limited, when the percussion note is duller and the respiratory sounds weaker, adhesions may be expected but are not always found. A long duration of the disease is no proof of the presence of adhesions. Even when adhesions are present and only a partial collapse can be attained, the symptomatic results may be gratifying. When the lung on the affected side is consolidated far less can be expected than when infiltration or even extensive excavation is present. The character and extent of the disease in the opposite side are of importance. Extensive infiltration may not prevent good results, provided dyspnœa is absent or very slight. An acute destructive process in both lungs is a contra-indication. When, however, more than a third of the less affected lung is infiltrated the collapse should be very gradual. The time may yet come when it will be held justifiable to collapse the lung of a patient admitted in an early stage who steadily fails in spite of all other treatment, and this even though the disease has not advanced beyond one lobe.

Complications.—These may be slight (subcutaneous emphysema), severe, or even fatal (gas emboli). Severe pain in the side with rise of temperature may occur, but effusion is far more common and occurs in 30 to 50 per cent. of the cases. It may become purulent (pus cocci or tubercle bacilli) and require treatment similar to tuberculous pyopneumothorax. When the effusion remains sterile it is wisest to replace it with nitrogen before the lung can expand and become adherent to the chest wall. Pleural reflex or pleural shock (a sickening pain in the

side accompanied in severe cases by vomiting and loss of consciousness) can be usually avoided by careful cocainization of the pleura.

Results.—The immediate results may be an increase of cough and expectoration with a rise of temperature, due to absorption of secretions that are shut up in the rapidly collapsed lung, which a gradual collapse may avoid. In a few days when good collapse is obtained the cough and expectoration cease or wonderfully decrease, the temperature becomes normal, and more slowly the pulse falls to normal. These results are maintained at first only as long as the collapse is kept up, but sooner or later, after a half to two or more years, the lung may be allowed to expand, provided no symptoms arise. When extensive excavation has taken place it is wisest to keep up the collapse indefinitely.

Accessories for Treatment.—The articles necessary for comfort while out-of-doors vary greatly according to climate, season, and individuality. It has been deemed wise to refer briefly to some of the appliances found to be of value after practical use. Inasmuch as in summer few or no wraps are required, this section will deal largely with the requirements needed in a cold climate, where, even when the thermometer falls below zero, the cold can be comfortably defied. As patients who undergo the outdoor treatment must live from six to ten or more hours in the open air, it is foolish to fit up a room luxuriously and neglect the porch, veranda, or wherever the patient passes his time out-of-doors. No detail should be omitted to make the porch comfortable.

Few climates are so perfect that protection against wind, rain, snow, or sun need not be afforded. Accordingly, revolving shelters, shacks, huts, porches, roofs, fire-escapes, have all been used. The porch, preferably facing south in winter, north in summer, should be roomy, and well protected by a roof and glass screens on one or possibly two sides, but never on three. The depth should be little greater than the height of the roof in front. It should be well lighted by electricity. Awnings may be used during summer. When occupied by more than one patient it should be so spacious that the chairs can be at least four feet apart.

A strong, comfortable, roomy, long, broad-armed chair, with a movable high back, provided with a good mattress and pillows with washable covers, and with a book rest or reading table, is a *sine qua non*. No chair is more comfortable than Dettweiler's, but the Adirondack Recliner is as comfortable and very much more durable. Metal chairs last little longer and are very heavy. A light wooden chair with a canvas seat can be obtained cheaply, and is very serviceable. Swinging chairs are less desirable, as the position is too readily changed. Hammocks constrict the shoulders.

In cold climates a fur coat, with a collar reaching above the ears, is a necessity, while fur rugs are more or less of a luxury. Steamer rugs are excellent, but horse or ordinary blankets and quilts answer every purpose. Sleeping bags are comfortable and should be made to come up to the armpits, front and back, opening in some cases down the front. Foot muffs lend great protection to the feet. A small table for the sputum cup, bell, books, writing materials, etc., is very important. On

exposed verandas wind shields are necessary. Foot warmers should, on account of chilblains, be avoided, if possible. Weak patients should never be allowed to wrap themselves up.

For Patients Confined to Bed.—The room, at least 10 x 12 feet, should have two windows, preferably in adjoining sides, reaching nearly to the ceiling (10 feet high). All ridges and corners should be avoided and the wall covered with washable paper or paint. The waxed floors, preferably of hard wood, may be covered with linoleum. Only one or two small rugs are advisable. All furniture should be well raised from the floor and, if upholstered, covered with leather or washable covers. Electric light and hot water or low pressure steam heating should be used. Coal-oil stoves should be avoided. Washable curtains, ending six inches above the floor, are not objectionable.

Opening out of one window which extends to the floor should be a porch, so arranged that the bed, wheeled out upon it, is fully protected from rain, wind, or snow. When for various reasons the windows cannot be sufficiently opened, "window tents" may be tried.

The bed should be of iron with a mattress of hair, air, or water. It should never occupy a corner nor stand with its head in a draught. A thin gauze screen placed in a window, which should not be closed, will often prevent a draught. A movable back-rest is important. A small bedside table for the cup, bell, urinal, etc., and a bed table, extending over the lap of the patient, are important.

For Patients Sleeping Out-of-doors.—When possible the bed should remain indoors until the patient is ready to retire, or, if possible, it should be heated with hot-water bottles, which, if well wrapped up, can be pushed to one side and remain warm for some time. Two mattresses, one preferably a box mattress, with paper between them; three to five pairs of double blankets, with a mackintosh sheet over them (protection against rain, etc.), or with a fiber blanket between them; a lambs' wool quilt and flannel or outing flannel sheets are all useful. The pillows should be arranged in the form of a V, with the apex at the head of the bed to receive the head of the patient, or, better still, three pillows should be used, one extending down either side, parallel to the body, and a third for the head. Some patients prefer to tuck the covers under them and so form a sleeping bag. Such bags may be used. To make a "Klondike" bed, put all the covers, except the counterpane, on the bed but do not tuck them under the mattress. Fold them under on each side until they touch in the middle or lap, if a tight "Klondike" is desired. At the bottom, the covers can be either folded under and laid on top of the mattress, as is done with the sides, or tucked under the mattress. Over this envelope place the counterpane and tuck it in tightly all around the mattress to keep the envelope of sheets and blankets from slipping off the bed should the sleeper be restless. If the pillows are placed in an inverted V, protection from the wind is given the head and neck. To get into such a bed, one must slide in from the top. On very cold nights it is wise to cover the pillow or bedclothes with a half-dozen small flannel squares, which can be removed one at a time when the breath freezes upon it, and to cover the face

with cold cream or vaseline. Woollen or outing flannel night garments, a cardigan jacket, sweater, or bath robe, a woollen hood covering the ears and extending down under the jacket, a domino mask (lined with flannel), bed-slippers, "boots" of flannel, may all be used.

Euthanasia.—When, after consultation with one or more physicians, it has been decided that all hope for recovery is past, and that three or four months of existence may elapse before death, it is in many cases kinder not to relax apparently any efforts directed toward overcoming the disease, but after some slight opposition, if need be, to acquiesce to the patient's wishes. Care should be exercised not to begin the hypodermic injection of morphine too soon, for fear it may lose its effect. Small doses (gr. $\frac{1}{16}$) night and morning lessen the dyspnœa, check somewhat the cough, and greatly improve the general comfort of the patient. The dose should be slowly increased. Inhalations of oxygen often give the greatest relief and should always be used for trying dyspnœa.

Results.—The results in general are encouraging. In the mind of the laity the former pessimistic view is replaced by the belief that every case of tuberculosis is curable. It is an easy task so to improve the general condition of a patient as to give him all the outward appearances of health, but it is a far different task to get him into such a condition that after a few months at work he will not relapse.

Pulmonary tuberculosis is a relapsing disease. The results must therefore be considered under two heads, immediate and ultimate. The immediate results may be manipulated, even unconsciously, but the test of time is rigorous, and "living" and "dead" admit of no personal equation or variation of definition.

Classification.—Patients must be classified on admission, on discharge, and according to the ultimate results. A classification should take into account not only the amount of disease in the lungs, but the actual condition of the patient. It must consider symptoms as well as the pathological and general conditions, for no one alone is sufficient. The personal equation should be eliminated as far as possible. The divisions, or classes, should be as sharply separated as possible and not too numerous, three being the number most widely advocated for many years. Prognosis and classification are closely associated.

Turban classifies patients wholly upon the physical findings. By this classification, Stage I includes those patients whose slight lesion does not exceed one lobe or two half-lobes. Stage II includes those whose slight lesion extends farther than Stage I, but at most to two lobes or a severe lesion extending at most to the volume of one lobe. Under Stage III are all not under I and II. "Slight lesion" is synonymous with infiltration and "severe lesion" with consolidation and excavation. Purely pleuritic dulness of slight extent is left out of account. Slight alterations in the breath sounds, *e. g.*, harsh breathing or prolonged expiration without change in percussion and without rales, are not to be considered. This properly balances both the extent and the intensity of the pathological changes, two factors, one of which is ignored in most anatomical classifications.

The best classification so far suggested is that adopted by the American

Sanatorium Association, and based largely upon Trudeau's and not upon Turban's. This is as follows:

1. **On Admission.**—These definitions indicate the farthest extent of disease and the greatest severity of symptoms that a patient can present and still belong to the stage defined. All patients beyond the incipient stage fall under the moderately advanced stage unless the physical signs and symptoms exceed those of the moderately advanced stage, when they should be classified as far advanced.

Incipient.—Slight or no constitutional symptoms (including particularly gastric or intestinal disturbance or rapid loss of weight). Slight or no elevation of temperature or acceleration of pulse at any time during the twenty-four hours. Expectoration usually small in amount or absent. Tubercle bacilli may be present or absent. Slight infiltration limited to the apex of one or both lungs or a small part of one lobe. No tuberculous complications.

Moderately Advanced.—No marked impairmen of function, either local or constitutional. Localized consolidation, moderate in extent, with little or no evidence of cavity formation; or infiltration more extensive than under incipient. No serious complications.

Far Advanced.—Marked impairment of function, local and constitutional. Marked consolidation of an entire lobe, disseminated areas of beginning cavity formation, or serious complications.

2. **On Discharge.**—*Apparently Cured.*—All constitutional symptoms and expectoration with bacilli absent for a period of three months; the physical signs to be those of a healed lesion.

Arrested.—Absence of all constitutional symptoms; expectoration and bacilli may or may not be present; physical signs stationary or retrogressive; the foregoing conditions to have existed for at least two months.[1]

Improved.—Constitutional symptoms lessened or entirely absent; physical signs improved or unchanged; cough and expectoration with bacilli usually present.

Unimproved or Progressive.—All essential symptoms and signs unabated or increased.

Dead.

3. **Ultimate Results.**—*Cured.*—All constitutional symptoms and expectoration with bacilli absent for a period of two years under ordinary conditions of life.

Well.—Patients who fulfil all the conditions required under "cured" but about whose sputum no definite information can be obtained.

Arrested. Improved. Progressive.—See above.

Dead.

Much opposition has recently been shown toward the use of "cure," and many hold that while pulmonary tuberculosis is curable it is impossible to say when a "cure" is attained, and that to apply

[1] The length of time mentioned is, of course, somewhat arbitrary, but is intended to cover the cases which frequently occur, in which the patients leave a sanatorium for various reasons, contrary to advice, after a stay of a few weeks, although all active symptoms may have ceased completely soon after entrance.

it, however modified, to patients is to give them a false sense of security. The use of tuberculin as a test of cure has been suggested by many observers. The results obtained in this way and by clinical methods do not agree, as many patients clinically "apparently cured" react to tuberculin. Nagel discharged 114 of 183 patients as clinically cured, and of these 114 patients, 38 per cent., reacted to tuberculin. Careful clinical observation determines sufficiently accurately whether or not a patient is "apparently cured."

Ultimate Results.—The real test is the division of all patients into two classes—living and dead. The division of the first class is difficult. Here ability to work is of most value, for it is difficult to obtain a physician's report on the general or pulmonary condition or on the sputum examination. An absolute cure can be determined only after death. At the Adirondack Cottage Sanitarium it is impossible to use this term "cured," for sufficient information cannot be obtained, and "well" has been substituted.

Statistical Reports.—The best statistical report is the one suggested by Turban, with the modifications adopted by the National Association. These consist in giving the side or sides of the lesion full data on discharge as well as on admission, and the figures for temperature, pulse, and respiration, instead of symbols. To collect a mass of statistics which will be of value, the Association further suggested that each sanatorium publish in its annual report the tabulation for each patient.

Results of Dispensary Treatment.—These are difficult to estimate. Many of the patients in early stages are sent at once to sanatoriums, some in more advanced stages go to hospitals, and the majority who undergo treatment at the dispensary are under more or less unfavorable surroundings.

Results in Sanatoriums.—The results of modern treatment are necessarily based upon the results obtained in sanatoriums, for results obtained outside of these institutions are seldom if ever given in sufficient detail to be of value. This also applies to the results at many sanatoriums which, started under adverse financial conditions, have published no report or given too meagre details to be of much value. Few sanatoriums, especially in America, have been in existence long enough to make the ultimate results of treatment very valuable. The time of residence in the sanatorium is of much importance for the result.

Results at the Adirondack Cottage Sanitarium.—A study of the results obtained shows at once the great value of early diagnosis in both immediate and ultimate results. Although the patients in the incipient stage were less than 28 per cent. of the total number, yet they furnished 69 per cent. of those apparently cured on discharge. Of patients in the incipient stage 14 per cent. are dead, while of those in the moderately advanced 43 per cent. and of those far advanced 81 per cent. are dead. Of the patients in the incipient stage discharged with active disease (*i. e.*, neither apparently cured nor arrested) five times as many recover, more than twice as many are alive, and only one-fourth as many are dead as those discharged with active disease in the moderately advanced

stage. Of all patients admitted in a far-advanced stage only 3 per cent. are alive and 1 per cent. are well. On the whole, the death-rate for the apparently cured patients may be said to be double the general death-rate. For patients discharged with arrested disease the death-rate may be said to be eight time the general death-rate.

The patients who were neither apparently cured nor arrested on discharge may be said to have on the whole a death-rate twenty-eight times the general death-rate. Roughly, over 50 per cent. of the patients in the incipient stage are alive fifteen years after discharge, while about 50 per cent. of those with moderately advanced disease are dead in six years. The classification by condition on discharge shows even a more striking picture. The ultimate results in those discharged apparently cured approximate rather closely the normal death-rate curve. The results in those discharged with arrested disease are far less encouraging. In six years over 50 per cent. are dead.

Loss of Physical Signs.—Complete disappearance of the physical signs is rarely attained, but has great bearing upon the ultimate results.

Weight.—The effect of sanatorium treatment upon the weight is strikingly shown in a study of 901 patients (453 males, 448 females) at the Adirondack Cottage Sanitarium. The weight of the men on arrival in the Adirondacks was 90 per cent. of their standard weight, that of women 91 per cent.; on discharge the men weighed 99 per cent. and the women 102 per cent. of this standard weight. Their usual weight in health was for the men 94 per cent. and for the women 95 per cent. of the true normal.

The Results in German Sanatoriums.—The results obtained at the sanatoriums founded largely by the German insurance companies are very striking when compared with the results obtained in all other diseases. The patients with pulmonary tuberculosis do slightly better the first and second years after discharge, nearly as well during the third year, while there is a decided advantage in favor of the non-tuberculous patients, which might be expressed as 6 to 5, during the fifth year after discharge. The women do decidedly better than the men, and the difference between the tuberculous and non-tuberculous patients is much less, due some hold to the less strenuous struggle for existence many of them lead. All relapsed patients are not readmitted, and, while the proportion refused is not stated, the figures would seem to indicate that fewer non-tuberculous patients relapse after the first year.

Children.—The results of sanatorium treatment in children are excellent. The figures show that children in incipient and moderately advanced stages do far better than adults, while those in far-advanced stages do worse (a matter of slight importance).

Results of Tuberculin Treatment.—No scientific basis for the very optimistic view of the tuberculin treatment that is at present widely gaining ground can be found in the vast majority of the results so far published. The figures seem to indicate that tuberculin treatment is of value and the vast majority of all who have used this treatment are in favor of it, while admitting in some instances the discrepancy between

their opinions and their figures. Few published statistics escape the error of selection.

Results of Tuberculin Treatment at the Adirondack Cottage Sanitarium.—The actual comparison of results is difficult, as the standards and number of patients treated have varied from year to year, but by reducing (or increasing) the numbers of treated and untreated for each year to 100 in each class the influence of varying numbers is eliminated. A study of 185 patients treated with tuberculin and 864 not so treated all of whom stayed over ninety days and had tubercle bacilli in their sputum on admission, shows for the incipient stage a slight difference on discharge in favor of the treated patients. For the moderately advanced stage a very marked difference on discharge in favor of the treated patients is observed (apparently cured, treated 27 per cent., untreated 6 per cent.; disease arrested: treated 50 per cent., untreated 51 per cent.: active, treated 18 per cent., untreated 43 per cent.).

The ultimate results obtained from one to fifteen years after discharge in 135 patients treated and 690 untreated, all of whom stayed over ninety days and had tubercle bacilli in their sputum, show that of 100 patients in the incipient stage treated with tuberculin 79 are alive, of the untreated 63 are alive, while in the advanced stage 61 of the treated patients are alive and 36 of the untreated.

Loss of Tubercle Bacilli.—Of all patients with tubercle bacilli in their sputum who undergo sanatorium treatment, only about 42 per cent. lose them. Any factor that can be introduced into sanatorium treatment to increase this figure is of great importance. Accordingly, if it could be shown that tuberculin caused the disappearance of tubercle bacilli in a greater number of patients, its value would be unquestionable, even if it did little else. Unquestionably the percentage of patients who lose their bacilli is larger among those treated with tuberculin. The disappearance of tubercle bacilli from the sputum depends directly upon the length of sanatorium residence. Tuberculin treatment can rarely be completed under five months, and in most institutions the patients receiving tuberculin remain on the average longer than the untreated. The care and accuracy with which the sputum is examined, as well as the frequency, has much to do with these results.

The treatment of pulmonary tuberculosis with tuberculin may therefore be said to be of value. It is of more permanent benefit to patients in moderately advanced than in incipient stages, and of slight if any value for those with far-advanced disease. The general nutrition of patients is little affected, but more lose their tubercle bacilli.

CHAPTER VII

LEPROSY

By ISADORE DYER, Ph.B., M.D.

Synonyms.—Lepra; Elephantiasis Græcorum, Hebræorum; Leontiasis; Satyriasis; Ophiasis; Tzaraath (Hebrew); Kushta (Indian); Juzam Dolfil (Arab); Fa-Fung, Ta-ma-Fung (Chinese); Boasi (South American); Llhata (South African, Bantu); Nsudi (Congo); Lebbra (Italian); Radesyge, Spedalsked (Norwegian); Aussatz (German).

Definition.—Leprosy is an endemic disease, contagious in type, due to the direct presence of the *Bacillus lepræ*, which in its development produces structural changes in the skin and mucous membranes, nerves, bone, and other tissues, usually resulting in more or less alteration in the configuration of the tissues involved, at times causing actual deformity and mutilation.

Occurrence.—There are few lands free of the disease, and it is estimated that there are nearly 3,000,000 lepers in the world. Of these, the largest number is in China (estimated at 2,000,000); the next is in India (estimated at 200,000); while the other parts of the world afflicted are the following: Japan (20,000 known lepers);[1] Africa; Madagascar; Arabia; Persia; Russia; Norway; Sweden; Italy; Greece; Spain (Germany, France, and Austria, excepting Hungary, are practically free of the disease); the islands of the Pacific and Indian Oceans. Leprosy is also endemic in Central and South America. The United States of Columbia, Ecuador, Venezuela, Brazil, Chili, and Peru have each recorded statistics concerning the disease. In Mexico and in almost all of the islands of the West Indies leprosy is found.

In North America a number of the United States are involved, notably Louisiana, California, New York, and Minnesota. In Louisiana the disease is endemic, occurring almost wholly among the native born or persons long resident in the State, while other centres show simply an increasing number of cases in recent years. Since 1905 about 400 cases have been recorded in the United States.[2] New Brunswick in Canada, at Tracadie, and British Columbia, at Darcy Island, have a few cases.

The numerical importance of the disease has carried considerable force with various governments, to the end that legislative action, aimed at segregation, control, and treatment, has become general. In some countries the provisions are fulfilled under private charity, but for the most part government provision of funds has accompanied the execution of enactments. These results have followed the Berlin Lepra

[1] *Transactions of the Berlin Lepra Conference*, 1897.

[2] "Leprosy in North America" (Dyer), *Transactions International Dermatological Congress*, Berlin, 1904. The author's notes record over 250 cases in Louisiana.

Conference of 1897, and in all countries an intelligent effort is now being made to accomplish a better knowledge of leprosy and its eradication, through sanitation and treatment.

Etiology.—Contagion.—The consensus of opinion has accepted the *Bacillus lepræ* as the cause of leprous lesions, and their effects and the evidence point to the introduction of the organisms of the disease through the nasopharynx. This theory is strengthened by the absence of an initial lesion of leprosy at any particular point of inoculation, the absence of specific inoculation or the history of such, and the frequent occurrence of the disease under conditions which favor the inhalation of the disease-bearing secretions from the original case.

Heredity.—Heredity is still held a factor by a few observers, but the vast majority have dismissed it as a consideration. The results of the British Leprosy Commission in India in 1893 showed less than 3 per cent. of cases developing among children of lepers removed at birth, and these showing the disease after the third year; the absence of any record of a leper born as such in any of the many centres of the disease still places the burden of proof on the few who claim this as a factor.

Race.—Race undoubtedly bears a close relation to the spread and to the element of susceptibility to the disease. Records in almost every country show the native born the most frequent victim, while the foreigner is slow to acquire the disease. There is no doubt, however, that the likelihood of exposure is more apt to occur in the family and community life among these, and must be taken into consideration.

Diet.—Quite a number of leprologists have urged diet as an element in the spread of leprosy and the prominence of some of these protagonists demands a consideration of the theory. Jonathan Hutchinson has supported the fish origin of leprosy for many years. His observations and deductions have been almost entirely derived from British India, and as yet the theory is unproved. Ashmead, Blanc, and others, have expressed a belief that fish may be the occasion of leprosy. Hutchinson propounds the idea that leprosy occurs chiefly in India among fish-eating peoples who are not particularly careful about the freshness of the food; others argue the possibility of fish acting as the intermediate host for the leprosy bacillus. As yet no one has discovered the bacillus of leprosy in fish or in any other food supply, and the disease occurs alike in those who eat fish and those who have no fish to eat. Almost as a unit the students of leprosy in India, the Hawaiian Islands, and in other lepra centres deny the evidence of any such origin. The observers in India point rather certainly to widespread occurrence of the disease among those castes who by religious obligations are forbidden fish.

Climate.—Warm climates evidently favor the development of leprosy, but it occurs in any climate, as is exemplified by the long prevalence in Norway, Sweden, Iceland, and Japan. Seaboard countries seem to have suffered most from the disease, but this is easily accounted for, as these are naturally most exposed through ordinary ways of commerce. Leprosy spreads, however, in every country where it is introduced. Where community life, hygienic environment, and standards of metabolism are high, the disease does not spread rapidly.

Vaccination.—Vaccination has been discussed as a probable method of the spread of leprosy, but no proof has followed the tentative theory, and in these days of bovine virus such a likelihood is precluded.

Insects.—Recently the proposition has been made that fleas might be the medium of spreading leprosy. Mosquitoes, bed-bugs, and other accidental parasites attacking the human body have been considered in the same way. E. S. Goodhue, of Holuloa, Hawaiian Islands, has found the *Bacillus leprœ* in mosquitoes and in bedbugs.

Other Diseases.—Fitch, of San Francisco, and some adherents argued the possibility of leprosy as a "fourth stage" of syphilis, but so many cases of syphilis contracted by persons already lepers have been reported that the theory has fallen, even if other evidence had not sufficed. The identity and correlation of leprosy and tuberculosis is a more recent idea which has been rather ventured than tried.

Morvan's disease, syringomyelia, and ainhum have been urged as types of leprosy, but the protagonists of such opinions have found their chief argument among cases, probably leprosy, with symptoms closely simulating these other diseases. Morvan's disease, however, was discovered and described in a Bretagne district, which later proved to be the ancient site of medieval leprosy, with numerous survivals of effete types of this disease.

While the contagiousness is capable of only indirect proof the vast amount of evidence points to this as the sole method of spread of the disease, and as more exact opportunity is now afforded to study early cases, it is likely that an initial lesion may be found.

Pathology.—Every evidence of leprosy in the human economy is essentially due to the lepra bacillus, no matter what organ is affected. This has been firmly established since the original discovery of the bacillus by Hansen in 1879. The *Bacillus leprœ* is described as a small rod bacillus, from one-half to three-quarters of the diameter of a red blood corpuscle in length ($\frac{1}{5000}$ of an inch) and in breadth about one-fifth the length. The bacillus is straight or slightly curved, with pointed or rounded extremities. It occurs in short chains or beads, resembling the tubercle bacillus, and may have its extremities club-shaped (Byron). The lepra bacilli are more abundant than the tubercle bacilli, and are more frequently found in clumps and masses in the tissues, and are more readily stained with the usual methods. In doubtful cases inoculation experiments establish the diagnosis of tuberculosis and exclude leprosy.

In animals, Damsch, Campana, and Vossius succeeded in reproducing the disease *in loco*, but not generally. Melchior and Ottmann succeeded in distributing the disease to the visceral organs, etc., following the introduction of a freshly extirpated leprous tubercle into the anterior chamber of a rabbit's eye. During the period between 1910 and 1912, Duval, Gurd, and Couret have experimented variously with white mice, white rats, turtles, fish, and monkeys. The inoculation experiments, on the whole, have been successful, but the strain of bacilli employed was of chromogenic type, and as yet not certainly the bacillus of Hansen.

Experiments with the human subject have been rare and without

authoritative verification (Daniellson and Boeck). The bacillus occurs in the nasopharyngeal and other secretions, the saliva, the feces, vaginal and urethral secretions, and in the semen, milk, and sweat. Sticker claims that the presence of the bacilli in such large numbers in the nasal secretion commends the early examination of this as a means to diagnosis. The fluid from artificial blisters as well as serum drawn from deep tissues have been examined for the bacilli with positive results.

The smears from these secretions and fluids are dried and fixed in the ordinary way, and stained with carbol-fuchsin, as for tubercle bacilli, decolorized with a weak solution of acid (3 to 5 per cent.), completed with alcohol and counter-stained with methylene blue. The cigar-bundle shaped masses take up aniline stains (Gram method) at the room temperature, and retain them tenaciously. Unna recommends staining in a twenty-four hour old Ehrlich's solution newly filtered for twelve to twenty-four hours at the room temperature or one to two hours in the incubator; wash for ten minutes in water, and place in 20 per cent. nitric acid until greenish-black. Wash in absolute alcohol until pale blue, and in water until colorless; dry and mount.

Attempts[1] at culture of the bacillus have met with varying results. The cultural possibilities of the lepra bacillus are still great, but the last utterance seems to leave the status of the bacillus and its culture in some doubt. Duval and Wellman[2] have announced that more than one strain of acid-fast bacilli can be cultivated by special methods from lesions of human leprosy, and they have drawn attention[3] to a non-chromogenic strain which differs from those isolated by Clegg, Rost, Bayon, and others, and which they consider deserves more serious attention than any organism so far described. It is not unlikely that most observers up to the present time have worked with mixed cultures, containing both the Clegg bacillus (chromogenic in type) and this newly described organism, which is not chromogenic.

The bacilli are widely disseminated throughout the body, having been found in practically every organ, and including the peripheral nerves, spinal cord, brain, and in the skin (even in scrapings of the skin), interstitial connective tissue and in the muscles. In general the number of bacilli has no relation to the severity of the accompanying tissue changes. Scheube[4] gives a summary of tissues where the bacilli have been observed.

Outside the human body the bacilli have been found in the habitations of lepers and in the ground over lepers' graves.

The leprous nodules belong to the group of granulation tumors, and are similar to those of syphilis and tuberculosis. Microscopically they consist of a small amount of fibrillar connective tissue with numerous cells of various forms, mostly small, round epithelial cells, spindle-formed, and the leprosy cells. These are mostly large, round, or oval

[1] Babes: "Die Lepra," Nothnagel's *Pathologie und Therapie*, 1901, Band xxiv, Wien. (A very complete bibliography on leprosy is given.)

[2] *Journal of the American Medical Association*, 1912, lviii, 1427.

[3] Jour. Infect. Dis., 1912, xi, No. 1, pp. 116 to 139.

[4] *Die Krankheiten der Warmen Lander*, IIIer aufl., Jena, 1903, pp. 320–392. (With a very complete bibliography.)

cells, with many nuclei and vacuoles. They contain the leprosy bacilli. These cells are diagnostic of the disease, and are found most numerously in the tubercles and nodules of leprosy. Virchow, Neisser, Gerlatz, and others argue the consistent type of the lepra cell as the container of the bacilli, the exception being against the rule; Unna is the chief protagonist of the "extra" cell theory, claiming that the lepra cell is only a mass of agglutinated bacilli, which are habitually aggregated in the lymph spaces.

In the trophic, or nerve type, the changes are found in the peripheral nerve trunks and their cutaneous branches, the central changes occurring secondary to general changes or infection. The leprous deposits are especially found in nodules along the ulnar, median, radial, musculocutaneous, intercostal, humeral, and peroneal nerves. Thickening of the nerve is common. The trophic changes follow the invasion of the nerve itself by the bacilli.

Symptoms.—The uncertainty of fixing any particular period of incubation and the lack of observation of the early stages of the disease compel a study of the preliminary symptoms only upon the subjective history, and after tangible manifestations are in evidence. Even in leprosy centres, suspicion of the disease arises only when local conditions appear and premonitory signs of the disease have been ignored. That they do exist many observers agree, and the arrangement of these is based upon a supposed period of incubation, as this cannot be exactly known. The history of exposure is usually absent, and, even when ascertainable, the length of time is too variable to admit of any accurate statement. This period varies from a few weeks to many years. Some instances are related in which twenty years had elapsed since known exposures to the disease had occurred. Continuous exposure over long periods has been noted, however, in the instance of several members of the same family or community being affected and here the prodromal symptoms have been studied.

The one most constant symptom is the occurrence of fever, intermittent and irregular in period and in type. Malaise, anorexia, dyspepsia, epistaxis, dryness of the nasal and respiratory passages, vertigo, headaches, neuralgias, pains in the arms and legs, and exaggerated functions of the fat and sweat glands are among the notable symptoms. The sweating is particularly striking, as it is periodical and evidently associated with nervous disturbances. There is in all instances a sense of anxiety, of anticipated calamity.

There may be marked hyperesthesia of the skin, shown in areas of pruritic exaggeration with localized neuralgias. The intestinal tract may be disturbed by frequent diarrhœa, and as a result it is quite usual for the patient to lose in weight.

So far as the specific manifestations are concerned, the usual diagrammatic method of resolving leprosy into fixed types is faulty and often misleading. While these certainly come under observation, the unusual cases are the rule. The evidences of leprosy are directly due to the invasion of the *Bacillus leprœ* and according as any particular organ or tissue is involved the symptoms are manifest. While any organ or

PLATE IV

Macules of Leprosy. (Leloir.)

tissue may be attacked, the vast majority of patients show the skin and the nerves as the selected sites.

Dependent directly upon the degree of this invasion and upon the individual resistance are the evidences in the skin and in the nerves themselves. If the skin shows the first evidence, this may appear in explosive lesions, as bullæ, in simple erythematous patches, or in exactly localized areas of bacilli colonized in masses and forming tubercles.

When the nerves are attacked, along the course of the nerve involved there is either thickening of the sheath or of the nerve itself, or nodes of varying size are formed. At the terminal ends of the branches of these nerves, skin lesions in the form of bullæ, pigmentation, thickening, or atrophy of the epidermis may appear, or there may be actual neuritic changes in the muscles, tendons, and bones.

Skin leprosy presents its several lesions either separately or together at the same time, and while the macule often occurs as a preliminary eruption it may be the sole evidence of the disease. So with the tubercles of leprosy. These may appear at once or may develop upon the areas previously outlined by the erythematous or macular eruptions. All of these lesions may occur together, and again they separately or together are often found concomitant with the nerve lesions and changes, which they may also precede or follow.

The first evidences of skin or nerve leprosy are the bullæ, found upon the extremities, especially on the hands and feet. With skin leprosy these are usually small in size, numerous, and superficial. They occur bilaterally and symmetrically, usually on the dorsum of the hands and feet, and especially over the fingers. They break quickly and dry, leaving a superficial erosion which heals spontaneously, and the site of the lesion is marked by a white scar, usually with a pigmented and irregular border.

With nerve leprosy these lesions are more often single, large, and occur over the joints of the phalanges; as a rule they persist, even ulcerating deeply at the point of origin. Even if healing should occur, there is a tendency for a new lesion to form at the site of the scar and ulceration develops, causing necrosis of the area affected. As any joint of any finger or of all fingers may be involved, the process may be progressively destructive, resulting in actual loss of one or more of the phalanges, either distal or intermediate. The process may start at the end of the digit, involve the nails, and result in the ultimate destruction of the whole digit, leaving the hand or the foot minus fingers or toes.

The erythematous eruptions are evanescent or permanent. In the first instance they occur as the evidence of a general infection, and come as an exanthem. They select particular regions, notably the cheeks, shoulders, buttocks, thighs, and legs, sometimes the arms, forearms, and hands. The eruption is bilateral, symmetrical, and marked by an irregularity in the size of the areas involved, which are sometimes no larger than the thumb nail, while again the area may involve the whole of the region affected, as over the buttocks. The patches are deep red in color, do not fade entirely on pressure, and have a suggestion of turgescence in a certain amount of elevation and rounding of the lesions.

In a few days or weeks these disappear and may not recur. Oftenest, however, the areas over the buttocks, thighs, legs, and shoulders remain defined as they first appear, growing dusky red in color, often mottled and thickening with age. The periphery grows more elevated and thickened, also increasing in depth of color to a brownish red, while the centre fades to a buff or even to a dirty white. The patches grow somewhat elliptical in shape, and remain in this general form and with this consistency throughout, or the borders break up into distinct masses of tubercles, each representing a colonized accumulation of the bacilli. When the face is involved there is often confluence of the erythematous areas, making a mask over the whole of the face and involving the neck and ears. Here the thickening destroys the normal expression and produces a fixed, satyr-like appearance giving rise to the term "*satyriasis*," sometimes applied to the disease. The nose, ears, lips, and eyelids become pendulous, occasioning a marked interference with the circulation and a consequent swelling. Ectropion follows, and a bleary stare results. With the general thickening the face rolls in folds and forms in parallel masses covered with a shining telangiectatic, smooth, or tuberous, sometimes fissured, skin; the lips grow swollen and everted, and "*leontiasis*" has developed.

Nerve leprosy seldom extends beyond the developments of the disease at the extremities. Here and there along the ulnar and sciatic nerves and their branches, on the surface of the skin an erythematous eruption may appear, usually only temporary and expressing some fresh leproma of the nerve. Of course the processes in nerve leprosy may go on at the same time that skin leprosy develops, and it is usual to see the one or other superimposed as the condition progresses. One rare instance of a correlation of nerve and skin leprosy is the atrophic type. Here, consequent upon the erythematous eruption and the pigmented areas, a general atrophy of the skin occurs, the muscular and keratin elements in large degree disappearing and leaving a true skin atrophy, with loss of the appendages, including the whole of the hair, the nails, and loss of function in the glands. Emaciation follows rapidly and death is swift.

Tubercle leprosy is essentially skin leprosy. The location of these lesions is not constant, but they have sites of predilection. The face presents these on the forehead, nose, alæ nasi, lips, chin, cheeks, and ears. The arch of the eyebrows is a frequent site. The hands and feet, legs, thighs, buttocks, shoulders, and forearms are the next in order of frequency.

The leprosy tubercle may be single, clustered, disseminate, or diffuse.

The single tubercle is usually large, more or less flat, and found on the face, cheeks, hand, or forearm; usually few occur. The color is bright brownish red with the centre of the flattened lesion lighter than the border. The clustered tubercle is usually rounded, closely aggregated, and selective of the alæ nasi, ears, chin, hands, and lower third of the leg; the buttocks may also be involved. These lesions occur with a classical bilateral symmetry, and are characterized by the almost olive and red color of the skin involved.

The *disseminate* leprosy tubercle is small, about the size of a pea, hard

PLATE V

Fig. 1

Satyriasis. Tubercular Leprosy. (Cooper.)

Fig. 2

Leontiasis. Terminal Stage of Tubercular Leprosy. (Cooper.)

Fig. 3

Single Lesions. Tubercular Leprosy. (Cooper.)

Fig. 4

Nodular Leprosy. (Cooper.)

and round, uniform in size, occurring generally over the body, bilaterally and symmetrically; the lesions are separated by areas of clear skin and distinguished from all other tubercles by the waxy white appearance, as if white wax showed through a dirty brown transparent covering. Almost always this type of skin leprosy argues the occurrence of like lesions in the thoracic and abdominal viscera, as these cases rapidly become acute and result fatally in short order.

In each of the varieties of skin and nerve leprosy, and especially in the former, there are periods of quiescence and exacerbation. A striking feature in the periods of exacerbation is the "lepra fever" mentioned by a number of observers. C. B. Cooper, Chairman of the Committee on Leprosy of the Hawaiian Government, has best described this phase of leprosy, although the condition seems more severe in his locality than elsewhere. He calls the condition "swollen head fever," as this was the term given it at the Hawaiian settlement at Molokai. He describes this as "an acute, epidemic, painful, inflammatory leprous fever, in which the head and face became greatly swollen, and in which the lymphatic and glandular systems become characteristically involved, especially the cervical and sometimes the axillary and inguinal glands as well." He was able to find the leprosy bacilli in the blood during the stage of fever. Concomitant with this condition is a typical lepra exanthem, differing from any of the eruptions above described. Cooper lays no stress on this, but, in the writer's observations at the Louisiana Leper Home, these were frequent enough to be considered important. The eruption consists in the occurrence, almost universally over the body, of bright red papules, lentil-shaped and uniform in size, usually hyperesthetic and at times painful, even severely so. With lessening of the general symptom, the eruption disappears, usually leaving, however, an increase in number in the previous lesions.

Lepra fever has occurred so frequently in connection with the eruption that Hopkins, in charge of the Louisiana Lepra Home, has ventured the opinion that they are reactionary lesions following a general infection from the degenerative changes in true lepromatous tubercles; in other words, that the papules and the lepra fever are a sort of "anaphylaxis."

Altered Sensation.—So much stress is laid upon this that special attention should be given to it. All skin lesions in leprosy excepting the evanescent erythema and the exanthem of papules in leprous fever are anesthetic to pain, sometimes to touch, heat, and cold.

Hyperesthesia is marked in the prodromal period and sensation is exaggerated in the exanthematous lesions. With nerve leprosy, hyperesthesia is marked for weeks and months before the evidence of an affected nerve is complete. This is shown in pain along the extremity, and in the hands and feet. Often distinct points of pain are recognized. As soon as the nerve is thickened and the nodes are formed, anesthesia becomes complete along the areas of cutaneous distribution of the nerve involved. Usually the anesthesia begins at the distal end of the nerve and travels toward the source. The little finger is usually the first point of anesthesia noticed, and more often on the left side.

Effete Leprosy.—The leprosy in Brittany and that in the Orient, as well as many cases found in old leprosy centres, present types which seem to show no acute symptoms at all, but which evidence trophic changes of slow development and unattended with inflammatory processes. They present the claw-hand, loss of phalanges, facial paralysis, etc., usually considered as sequelæ of nerve leprosy.

Sequelæ.—As the direct result of leprous changes in the body, destructive processes in the internal organs, ultimately producing death, may result. Hillis tabulates the causes of death as marasmus (38 per cent.), septicemia or intercurrent disease, as nephritis (22.5 per cent.), pulmonary diseases, including tuberculosis (17 per cent.), diarrhœa (10 per cent.), anemia (5 per cent.), remittent fever (5 per cent.), and peritonitis (2.5 per cent.).

The natural necrosis, attending the final degeneration of tubercles, results in the loss of the nasal bones, often of the nose itself; in the ulceration on the face, and in involved areas there is scarring, with contracting cicatrices, producing facial and other deformity. Most trophic nerve types develop one or more ulcers at the extremities, with consequent destruction of tissue. According to the limit of the process there may be simple contraction of muscles, atrophy of bones, and subsequent deformity, or the whole of the member involved may slough off.

Diagnosis.—The customary observer of leprosy needs little aid to a diagnosis, as the facies, the color, and the classic lesions are well known to him. So much responsibility, however, rests in determining leprosy that due care should be exercised by those to whom it is a casual disease.

The diagnosis is absolute when destructive lesions exist in which the lepra bacillus may be demonstrated in section, in the fluid contents, or in culture. Clinically there should be little difficulty if the cardinal features of the disease are kept in mind. The essential points may be summarized as follows:

1. The habitat, community, or domicile, suggesting exposure.
2. A history of exposure or contact with persons affected.
3. Eruptions or bullæ on the extremities.
4. Areas of discoloration with anesthesia.
5. Trophic disturbances: (*a*) Perforating ulcers; (*b*) muscle atrophy, especially of the hands, determining the "claw-hand;" (*c*) clubbed fingers; (*d*) deformity of the hands and feet from loss of phalanges; (*e*) persistent ulcers at the articulations of the phalanges of the fingers and toes; (*f*) facial paralysis.
6. Discolored and blunted nails.
7. Symmetrical eruption of macular areas with bilateral distribution: (*a*) Marked by dusky red or "café-au-lait" discoloration; (*b*) with elliptical shape, the peripheral ring being elevated and deeply pigmented, while the centre remains lighter or a dirty white in color; (*c*) marked anesthesia throughout these macular areas; (*d*) a predilection for particular regions, notably the buttocks, legs, and forearms.
8. Tubercles with typical modes of appearing and of distribution.
9. Loss of expression in the face; satyriasis, leontiasis; ectropion of eyelids and of lips; furtive look in the eyes.

10. The early involvement of the nasopharynx and the larynx, resulting in a characteristic involvement of the vocal cords, determining a peculiar metallic resonance in the speech, which is distinctive.

Particular diseases mistaken for leprosy are few and the differentiation easy: *Erythema multiforme* presents lesions which are evanescent, fade on pressure, without pigmentation, and are not anesthetic. *Syphilis* is differentiated by the color of the lesions, the symmetrical distribution of the leprous tubercles, their anesthesia, and course of development. *Sarcoma* (multiple) by the pain, the size and course of development, the color and consistency. *Lupus vulgaris* by the color, distribution, consistency, and method of development of the lesions. The examination of the section or culture is sometimes necessary. *Morphea* by the absence of anesthesia and the color. *Raynaud's* disease by the progressive ulcerative process, limited to the extremity involved, and by the absence of the nerve-trunk involvement. *Syringomyelia:* So many observers have related cases of leprosy possessing all the features of this disease, and it so often occurs that cases diagnosed as syringomyelia are subsequently proved leprous, that it is impossible to differentiate these except through finding the lepra bacillus, or postmortem evidence of changes in the cord without leprous involvement.

Prognosis.—Leprosy is like all other bacillary and infectious diseases; it is self-limited. Its evidences may last for years, or only for weeks or months. Often the disease will have periods of abeyance and exacerbation. Most often the course is run to a fatal issue or the victim may present scars or mutilation as the final expression of the spent morbid process. The average duration is about eight years. The mixed and tubercular are the more rapidly concluded, in from four to twelve years, unless shortened by some intercurrent disease. The spontaneous involution of lesions may be followed by no recurrences, but this is usually only a process in the final result, though the longevity of the individual may be increased by this remission.

Treatment.—Until recent years the sole treatment was directed to sanitary control, in some countries administered under barbaric restrictions and methods. Today most countries afflicted with the disease are provided with hospitals and asylums, the majority of these being under hygienic regulations so far as habit and food are concerned. In some instances leprosy has been reported cured. The most striking thing in the reported cures is the variety of remedial measures employed.

In all cases under treatment the progress in amelioration is slow. On the other hand, the disease may be absolutely self-limited without treatment, disappearing without a relapse or recurrence. The result of treatment depends directly upon the individual patient, and upon the resistance he possesses or may acquire against the morbid process. The treatments which have availed most have been supportive and hygienic. Drastic or reducing methods have been temporarily remedial, but the disease reawakens usually in the depleted subject. Serum and vaccine treatments have been attempted, but hitherto have been successful almost solely in the hands of those introducing them.

The treatment of leprosy may be arranged in several divisions

according to the method employed, viz., alterative; supportive; empirical; serum or vaccine; sanitary; and surgical.

The alterative treatment has been based upon the idea that such medication would reduce hyperplastic conditions and aid their absorption. Remedies so employed have been bichloride of mercury (Crocker), salicylate of soda and salol (Hawaiian Islands), europhen (Goldschmidt), chlorate of potash (Chisolm, Carreau), and the iodine salts. The results have been variable, though Crocker has reported 2 cases and Hutchinson 1 case evidently cured by hypodermic injections of the bichloride of mercury; Goldschmidt used europhen hypodermically successfully and Gruenfeld of Odessa confirmed this result; all of these cases have been isolated instances, however, arguing the first conclusion that the resistance is the essential factor.

Supportive or tonic treatment includes such remedies as hoang-nan, strychnine, arsenic (Hutchinson and G. H. Fox), mercurial salts, general tonics, each of these having a particular champion for the time being.

Empirical treatment has had a continuous history, even to the present, when every now and then some new discovery is brought out. India has supplied most of the drugs employed. Chaulmoogra oil seems to have survived almost all the other herbaceous remedies, and is now extensively employed. The dosage depends upon the patient, but to be effective should be increased to 100 to 150 drops at the dose, or 300 to 450 drops a day. Beginning with 3 to 5 drops of the oil in capsule, coffee, hot milk, or cordial, the dose may be increased gradually to tolerance. The oil may be given in pill form, combined with tonics, as iron, arsenic, and strychnine, or nux vomica. More cures have resulted from its use than from any other one remedy, and within a few weeks after its use amelioration is noted, even in advanced cases.

The Fiji Islands practice a scorching process which has its merits: The patient is placed upon a pyre of green leaves of a tree supposed to be specific against leprosy. In the slow process of cooking which the skin receives, the disease is supposed to disappear, and if the victim survives, he is expected to recover. The Japanese employ local measures of similar effect in the shape of "moxa"—resembling "punk" or oakum. These are stuck on the local lesions with a sort of glue, and then are ignited. As they finish burning a local eschar is formed.

The West Indies and some parts of South America carry the superstition that the bite of a venomous reptile will cure leprosy, and occasionally a native victimizes himself to this end. Influenced by the report of the condition resulting from the accidental biting of a leper by a viper in the West Indies, the writer used the antivenomous serum of Calmette in a series of patients, with almost uniform good results. Three of the patients recovered. Injections were made at frequent intervals, sometimes daily, and the dosage varied from 5 to 20 cc. The buttocks and the shoulders were the usual sites of injection, though frequent injections were made in the lesions themselves, with the interesting result that these were directly influenced to favorable resolution.

The sera of Carrasquilla and of Laverde, derived from the leprosy bacillus and tissues, may be mentioned. Both were successful to a

greater or less degree at the hands of the originators, but failed elsewhere. More recently a new serum was introduced by Rost of the Indian Medical Service. This, which he called "leprolin," was derived from a toxin of the *Bacillus leprœ*. In every patient under treatment marked improvement was noted, and of 120 cases treated, 14 were discharged as cured, and a number of others were reported as improved. Later, Rost reported relapses in all cases treated, and abandoned his remedy. Duval has reported a vaccine for leprosy, but the experience as yet lacks results enough to warrant any extended use of the remedy. Wellman has reported results from the use of salvarsan employed in early cases.

Treatment resolves itself into the essential fact that the disease is one in which a method of reconstruction is necessary, based upon hygiene, diet, and medication. Experimental treatment should be secondary to well-known practice, and only when evidence of improvement under recognized treatment is absent. Treatment above all must be constant and the patience of both physician and the patient must be great.

The regular practice with the writer is to insist upon daily hot alkaline baths, a liberal diet without indigestible food, and a regular dosage with strychnine in $\frac{1}{60}$ to $\frac{1}{30}$ gr. doses. Arsenic, iron, the phosphates, olive oil, etc., are given selectively. The majority of patients are treated with chaulmoogra oil, but now and then some other treatment is indicated. Under this general regime, more than 25 cases of leprosy have been cured since 1894.

Surgical treatment is directed to the condition present and consists in amputations, nerve-stretching, and electrotherapy. The use of *x*-ray treatment may be mentioned. Gilchrist succeeded in reducing the tubercles after a number of exposures.

So far as concerns the United States in the general sanitary care of leprosy, Congress has enacted several bills, directed at the investigation of the disease, and in February, 1905, a bill was entertained looking to a national leprosarium. As yet nothing has come of this. Meantime, Louisiana regularly cares for her lepers in a model home under hygienic and systematic medical administration; Massachusetts has established an asylum for lepers on an island in Boston harbor; Texas has promulgated a law requiring the report and isolation of lepers. The rest of the United States takes little interest in the subject, excepting San Francisco, where a large Chinese contingent compels a system of segregation.

Earnest efforts throughout the world promises relief from the disease in one or another way—either by obliterating it by segregation or of finding a systematic cure.

CHAPTER VIII

INFLUENZA

By FREDERICK T. LORD, M.D.

Classification.—Influenza may be classed as (1) pandemic influenza, (2) endemic-epidemic influenza, and (3) sporadic influenza. If the influenza bacillus be regarded as the sole cause of true influenza, the disease may be designated influenza vera when this organism is present, while those cases with a similar clinical picture, but in which the influenza bacillus cannot be found, may be classed as influenza nostras or grippe. The specific relation of Pfeiffer's influenza bacillus to influenza still needs confirmation, however, and the question may not be settled before another pandemic. Until the etiology of the disease is finally determined it seems best to use the term influenza to designate, a complex of symptoms without regard to the apparent bacterial cause.

Epidemiology.—It is difficult to trace the origin and course of the different epidemics, especially the earlier ones. Some of the great pandemics, notably the last, afford evidence of a general direction from east to west. The distribution of the disease has been variable, from local to general diffusion, at times covering the greater part of the globe as true pandemics. Even before 1889–90 it was noted that the disease prevailed without relation to the climate, wind, weather, or telluric conditions. In rapidity of progress the outbreaks exceed that of any other known disease, and were thought too rapid to admit of contagion from person to person. A careful statistical study was made of the last great pandemic, and valuable data were obtained by numerous collective investigations.

The origin of the 1889–90 pandemic, like many others, is uncertain. The outbreak in Hongkong in the fall of 1888, in Buchara in the middle of May, 1889, or in Tomsk in the beginning of October, may have been the starting-point of the epidemic which occurred in St. Petersburg toward the end of October. By November the disease had swept through Germany and France; by December through Austria, Sweden, Denmark, Switzerland, Italy, Spain, Portugal, Belgium and the Netherlands, England, the Balkan States, and North America. By March it had reached India and Australia; by April and May, China and the Gold Coast of West Africa. Berlin was invaded the middle of November, Paris from the 17th to the 20th of November, London the second week of December, Boston and New York the 17th of December. Within a year it had visited nearly all parts of the world.

Scarcely was the pandemic of 1889–90 ended when small local outbreaks reappeared in a few places. In the winter of 1891, however,

an extensive epidemic occurred in the United States and the North of England, but seems largely to have spared Europe, with the exception of small scattered local outbreaks. A direct relation between these isolated infections could not be established, and they seemed to come from local sources. Again in the fall of 1891 and spring of 1892 there was a third outbreak, this time again reaching the proportions of a true pandemic.

A study of the reports of the first great pandemic of 1889–90 from all parts of the world showed that the disease had not spread, as had been previously believed, faster than modern modes of conveyance, but rather followed the lines and did not exceed the rapidity of human intercourse. A succession of scattered cases preceded and led up to the epidemic in the regions attacked. The principal commercial cities or larger garrisons were first invaded, then the smaller places and the neighboring country. On boats the disease first appeared after touching at an infected port. Institutions little in communication with the outside world, such as prisons, convents, and lunatic asylums, were often spared or affected later than the neighboring population. When cases did occur they were at first often exclusively among those having intercourse with the outside world. Thus the great mass of evidence is in favor of the direct transfer of the disease from person to person.

In the two later epidemics a more irregular course was followed; the spread from place to place could no longer be traced. The disease diffused more gradually and lasted longer in a given neighborhood. Fewer persons were attacked. Not a year has elapsed since the last great pandemic without local outbreaks in some part of the world. The most widespread epidemic in the United States occurred in the winter of 1907–08. The writer[1] found that about 100 of 600 employees in one department store in Boston were affected. Davis[2] estimated that nearly one-third of the inhabitants of Chicago were attacked.

Morbidity.—In general about 40 per cent. of the population were attacked in the first great pandemic, thus repeating the experience of previous outbreaks and maintaining a record equalled by no other disease. Though no age is exempt, infants and old people seem least disposed to infection. Males and the robust members of the community seem more susceptible, probably because of their more frequent exposure.

Duration of Epidemic.—The invasion period, from the recognition of the first cases to the beginning of the epidemic, was usually fourteen days. In a given locality the epidemic commonly lasted for four to six weeks, allowing two to three weeks for it to reach its height and an equal period for its decline.

Meteorological Conditions.—There is but one plausible relation—that of the seasons. Of 125 independent epidemics, collected by Hirsch, 50 began in the winter months, 35 in the spring months, 16 in the summer months, and 24 in the fall months. Once developed the disease seems to run its course equally through all the seasons. Its more frequent

[1] *Journal of Medical Research*, 1908, xix.
[2] *Arch. Int. Med.*, 1908, ii, 124.

onset in the colder months may perhaps be explained by a lack of sunshine, for Ruhemann finds that the number of cases of sporadic influenza is greatest when there is least sunshine.

Immunity.—Unfortunately we know little about immunity in influenza. Statistical studies of institutions on this point are rare, and it is to be hoped that in recurring epidemics more data will be obtained. Population immunity may explain the freedom of the European continent in the spring of 1891, while influenza was epidemic in the United States and the North of England. It may also account for the smaller proportion of persons attacked during the isolated epidemics which followed the pandemic and the gradual dying out of the disease in epidemic form. Variation in the virulence of the infecting organisms may likewise be a factor.

Influenza in Animals.—No definite relation has been established between epidemics in man and in animals.

Etiology.—In 1892, Pfeiffer[1] published his preliminary communication which was followed in 1893[2] by his more elaborate report. The organisms were found in all the uncomplicated cases in pure culture in the sputum. When stained they appear as minute rods, two to three times as long as broad, often in great numbers in and between the pus cells. Their ends are rounded and usually take the stain more deeply than the middle. They have no capsule and do not stain by Gram's method. They grow only in the presence of hemoglobin, and cultures may be most conveniently prepared by pricking the previously sterilized dorsal aspect of the thumb, just above the nail, and smearing the blood on the surface of plain agar slants. After twenty-four to forty-eight hours in the incubator, if the culture is pure, minute, transparent, dew-drop-like colonies appear, often visible only with a hand lens. They show little tendency to confluence. Under the microscope they are structureless.

The influenza bacillus is strongly aërobic. No growth takes place above 43° or below 26° to 27° C. In sterile tap water at room temperature growth does not occur after thirty-two hours. On blood-agar viability is lost, after fourteen to eighteen days, whether at room temperature or in the incubator. On repeated transplantation, however, especially in symbiosis with the staphylococcus, growth may be indefinitely prolonged. From dried sputum no growth can be obtained after thirty-six to forty hours. Spore formation has not been observed.

Pathogenesis.—**Animals.**—Pfeiffer was unable to cause a true infection in many experiments on mice, rats, guinea-pigs, rabbits, hogs, cats, dogs, and monkeys. Isolated examples of animal infection are found in the literature. Wollstein[3] succeeded in producing a severe and fatal meningitis in monkeys by intraspinal injection.

Human Infection.—The finding of influenza bacilli as the sole infecting agent in pulmonary and extrapulmonary lesions affords valuable confirmatory evidence of their power for human infection. Confirmation of the pathogenic power of the organism from the presence of a specific

[1] *Deut. med. Woch.*, 1892, ii, 28.
[2] *Zeit. f. Hygiene*, 1893, xiii.
[3] *Journal of Experimental Medicine*, 1911, xiv.

PLATE VI

FIG. 1

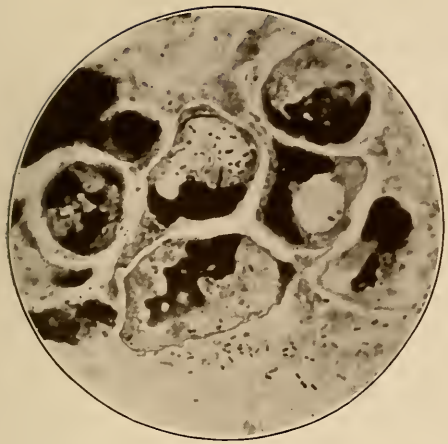


FIG. 2

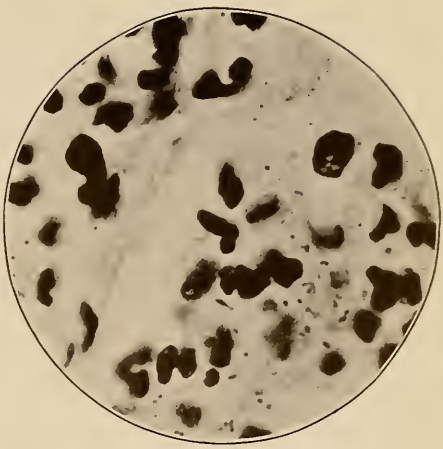


FIG. 3

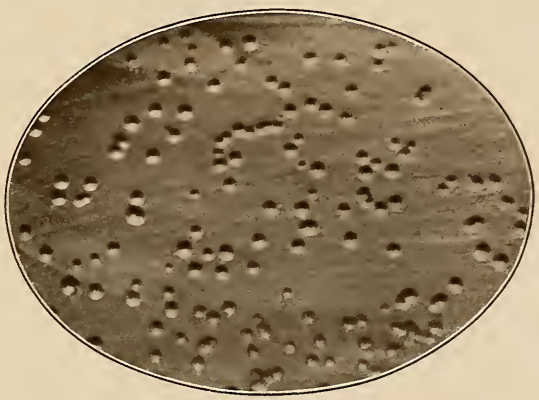


FIG. 4

FIG. 5

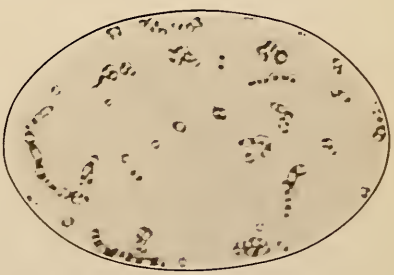


Fig. 1.—Influenza bacilli in sputum. × 1000.

Fig. 2.—Influenza bacilli in alveolar exudate. × 1000.

Fig. 3.—Culture of influenza bacilli on blood-agar (low magnification).

Fig. 4.—Smear preparation of influenza bacilli from culture. × 1000.

Fig. 5.—Smear preparation of influenza bacilli from culture, showing the occasional larger size of the organisms and their safety-pin appearance. × 1000.

reaction has not yet been established. In a series of such experiments, the writer found that the necessary dilution was low, that the reaction was very inconstant, and that the blood of apparently uninfected individuals also produced clumping.

Specificity.—The influenza bacillus, contrary to Pfeiffer's original observations, has been found in interepidemic periods, with or without influenza, by a great many investigators. It is not only a very frequent infecting agent in cases of acute respiratory disturbance during the interepidemic period, but may even be found in many cases of chronic cough, the origin of which in an acute attack cannot be established, as was shown in the writer's cases.[1]

The most natural speculation seems to be that the great prevalence of influenza bacilli in interepidemic periods serves to bridge the gap between recurring outbreaks. Until proof can be offered to the contrary this must be assumed to be the explanation; but their relation with the disease rests only on their presence and more often in the severe cases with bronchitis and bronchopneumonia. They are frequently found in cases without a typical clinical picture of influenza, and the disease cannot be produced experimentally in animals. It may be that they are secondary invaders, and that the true cause is yet unknown. The solution of the problem may not be accomplished until the next pandemic and the necessary confirmation of Pfeiffer's belief in their etiological relation with the disease. On the other hand the clinical and pathological picture caused by infection with other organisms cannot be differentiated from infection with influenza bacilli. The same symptoms of onset and course, a like degree of prostration, and similar pulmonary sequelæ, are common to them all. It may be, therefore, that other common respiratory organisms can set up epidemic as well as endemic infection. We must otherwise assume a different biological peculiarity for the influenza bacillus, enabling it alone to reach epidemic and pandemic prevalence, either through increase of susceptibility on the part of the host or increased virulence of the organism.

During the epidemic in Boston in 1907–8 the writer found the influenza bacillus in practically pure culture in the sputum in only 3 of 20 cases. Among 24 cases reported by Davis from Chicago this organism was present in only 4.

Pathology.—Because of the low mortality, observations on the pathology of the disease are not numerous. Our knowledge of this aspect is largely confined to changes occurring in the respiratory tract or its adnexa.

Swelling and injection of the nasal mucous membrane, with mucopurulent secretion, may be noted. Weichselbaum constantly found a purulent inflammation of the nasal sinuses. The frontal and ethmoid sinus and the antrum of Highmore may be invaded. Otitis media is frequent. Meningitis may occur. Inflammation of the larynx, trachea, and bronchi may also be present.

In the lungs the typical change is bronchopneumonia, in isolated

[1] Lord, *Boston Medical and Surgical Journal*, May 11 and 18, 1905.

patches separated by air-holding tissue. The confluence of neighboring areas may resemble croupous pneumonia on superficial examination. On inspection, in the centres of the involved lobules grayish-yellow pin-head to pea-sized slightly elevated foci may be seen, surrounded by engorged pulmonary tissue. On pressure, a greenish-yellow thick pus may exude from the infiltrated tissue or the cut ends of the bronchi. On microscopic examination, the bronchial epithelium may be found lying free in the lumen, separated from the submucosa. The smaller bronchi may be entirely filled with leukocytes with complete absence of epithelium. The peribronchial connective tissue may likewise be infiltrated with cells. Enormous numbers may crowd the neighboring alveoli for varying distances from the affected bronchi and completely efface the normal pulmonary structure. The cellular character of the exudate is usually very striking, but varying amounts of desquamated epithelium, serum, and fibrin, are present. The fibrin, however, is much less abundant than in croupous pneumonia.

Great numbers of influenza bacilli are found in and among the pus cells of the bronchi and alveoli in the areas of most marked bronchopneumonia. They become less numerous as the periphery of the lobular process is approached.

Abscesses.—In the microscopic sections of influenza pneumonia it is not infrequently noted that the alveolar septa are absent in small areas of most marked cellular infiltration, apparently forming the beginning of small abscesses. In a smaller number the cells in these places may be necrotic, suggesting the impossibility of full restoration to normal. Smith noted softening with abscess formation in sections from 1 to 5 cases. Well-marked pulmonary abscesses were present in 2 of 13 cases of influenza bronchopneumonia studied by the writer.

Induration.—In subacute or more chronic cases an increase of connective tissue can be observed. In Weichselbaum's 8 cases of bronchopneumonia in which he demonstrated influenza bacilli he observed a more or less advanced pulmonary induration in 3. In the writer's 13 cases pulmonary induration was present 7 (macroscopic in 3, microscopic in 4).

Symptoms.—Incubation Period.—The interval between exposure and infection is undoubtedly short. In Parson's returns it was fixed usually at two to three days; in rare instances from a few hours to a week or more.

Typical Influenza Attack.—Prodromal symptoms are usually lacking. Most attacks begin suddenly. An initial chill or chilliness is followed by fever, headache, and general pains. Malaise and prostration are usually striking. Catarrhal respiratory symptoms, commonly limited to the upper part of the tract occur so frequently that they must be regarded as a part of the characteristic picture.

Disturbances referable to various organs may occupy the foregound, constituting the respiratory, nervous, and gastric forms of the disease. In rare cases influenza may apparently occur as a simple fever, of short duration, without localization of the process. Various combinations of the different forms may appear in isolated cases, thus complicating

the picture. The disease may present a different clinical picture at different times or in different places. Variations from the simple, uncomplicated type were more common in the succeeding epidemics than in that of 1889–90. In children the clinical picture may be even more variable, with a larger proportion of serious initial nervous phenomena. The duration of the simple and typical attack does not usually exceed one to several days. Convalescence is rapid in most cases but may be slow even after a mild infection.

Types of the Disease.—Despite its vagaries, the prevailing picture of the disease in all epidemics has been that of a respiratory infection. In Vogl's 278 cases from the last pandemic, the "overwhelming majority" had catarrhal symptoms in the nasopharynx, trachea, or bronchi. Eight were fatal from disease of the respiratory tract. The mortality returns from most of the large cities, before, during, and after the epidemic, show that influenza has left its impression on them only in an increase of deaths from respiratory disease, which marks off with almost unfailing accuracy the prevalence of an epidemic in a given locality. A striking increase in the number of cases of inflammation of the middle ear during the epidemic still further fixes the respiratory tract as the place of election for influenza. It seems probable, therefore, that respiratory infection represents the type of the disease. Symptoms arising in connection with other organs may be infection proceeding from an unrecognized portal of entry in the respiratory tract, or may be due to toxemia. The local lesion may be slight and easily overlooked in the predominance of nervous, gastric, or febrile disturbances.

1. **Respiratory.**—The onset is like that in other acute diseases. The catarrhal process may begin at any part of the tract and remain localized, or spread by continuity. The upper air passages are more frequently involved. Prostration is often strikingly out of proportion to the local lesion. In mild cases the symptoms may rapidly subside. In more severe attacks the secretion is abundant and the whole tract may become involved. The fever continues; there may be delirium and great weakness. With invasion of the deeper parts, cough may be very distressing, with dyspnœa and cyanosis.

Rhinitis.—Coryza is perhaps the most common symptom. It may be accompanied by anosmia and conjunctivitis. Extension of the inflammation to the ethmoid cells, the frontal or sphenoidal sinus, and the antrum of Highmore, is common in severe infection. Distressing frontal headache or facial neuralgia may result. Influenza bacilli, mixed with other organisms, have been demonstrated in all these regions.

Tonsillitis.—Rawness of the throat, with redness of the tonsils and slight enlargement of the cervical glands, is common. The general symptoms may be severe, but marked local changes are rare. Tonsillitis was reported in only 3 per cent. of the 287 Bavarian army cases. Influenza bacilli are usually mixed with others in tonsillar infection, and in some instances the process may apparently be mistaken for diphtheria. Jehle regards the tonsils as the portal of entry for infection of the blood, finding influenza bacilli in their parenchyma and not elsewhere in the respiratory tract in 3 of 7 cases of septicemia.

Laryngitis.—Laryngitis may occur; at times the infection is severe, with fever, hoarseness, aphonia, and dyspnœa. Œdema of the glottis has occurred. Tracheitis is frequently present and may be accompanied by substernal tickling and burning sensations.

Bronchitis.—Bronchitis usually results by extension from above, and is a very important manifestation. The cough is at first dry and the sputum scanty. If the finer bronchi are invaded the cough is more distressing and may be paroxysmal. Dyspnœa may be a troublesome feature and cyanosis may be marked. The temperature is usually elevated, falling to normal in favorable cases within a week. If only the larger tubes are involved there may be no objective signs. It is more common, however, to find rales throughout the lung and more marked at the bases. They may be localized at the apices, and the subacute or more chronic cases are not infrequently mistaken for tuberculosis. When localized rales persist at one or more places, bronchopneumonia should be suspected.

The sputum becomes more abundant after a few days and contains greenish-yellow purulent masses. The character of the sputum is not distinctive of infection with influenza bacilli. In the more severe cases the cough and expectoration usually continue with gradually diminishing severity for six to eight weeks. Though the excretion from the upper parts of the respiratory tract usually shows a mixture of various organisms, that from the bronchi and lung at first often contains a pure culture of influenza bacilli; but as the process clears up and the amount of sputum diminishes, other organisms are likely to appear.

Bronchopneumonia. This is one of the most important manifestations. Its frequency is difficult to estimate and it is probably more common than statistics show, not only because of the readiness with which small patches may be overlooked, but also from the failure of many observers to class pneumonia as a manifestation of influenza. In practically all series of cases, both lobar and bronchopneumonia are included. Of the 55,263 German army cases, 534 (0.97 per cent.) had pneumonia.

The lungs are usually invaded by extension from the bronchi, but may apparently be primarily involved. When preceded by bronchitis the pneumonia seldom begins until after the fourth day. Its onset may be indicated only by an increase of the existing symptoms. It is rarely abrupt and the initial chill is uncommon. The pleural pain of croupous pneumonia is often absent. There is increase of the dyspnœa and the sputum is at times blood-tinged; but the rusty sputum of croupous pneumonia is not seen in uncomplicated bronchopneumonia. The expectoration is often made up of discrete greenish-yellow masses surrounded by mucus. Similar suptum is seen in pulmonary tuberculosis and after infection with other organisms than the influenza bacillus. Influenza bacilli can often be obtained in pure culture from the well-washed purulent masses.

The temperature may be only slightly elevated, is often irregular, and usually terminates by lysis after a variable period. In severe cases it may remain elevated for weeks. Sweating is frequent. Solidification may occur at any part of the lung. The foci may be multiple or confined

to a single area no larger than the bell of the stethoscope. The lower lobes are more frequently affected.

The diagnosis is often difficult or impossible, unsuspected consolidation being found at autopsy. Objective signs may be limited to persistent rales at one or more places. Bronchial breathing may be present without dulness, if the solidification is central. In more superficial processes, there is bronchial breathing, with dulness, increased vocal and tactile fremitus, but the signs are likely to be more atypical than in lobar pneumonia. Plugging of the bronchi may cause atelectasis, with the signs of pleural effusion over limited areas. If the bronchial occlusion can be removed by cough the signs may disappear. In doubtful cases exploratory puncture should not be delayed.

Signs of solidification often outlast the rise of temperature. Resolution may be very slow and yet finally end in symptomatic efficiency of the lung. In one case of influenza pneumonia followed by the writer, the bronchial breathing disappeared only after six months, and there are now no signs of disturbance.

Abscess and Gangrene.—Though complete resolution may follow influenza pneumonia, it is very common in fatal cases to note small losses of pulmonary substance. The necrotic foci are usually small and may be suspected during life only by signs of localized bronchitis. By extension or the fusion of neighboring areas, larger losses of substance may occur. Among Fraenkel's 80 cases of influenza pneumonia were 6 of pulmonary gangrene. The sputum is foul and contains elastic fibers. Influenza bacilli are usually mixed with other organisms, but Hitzig reported a case of pneumonia followed by abscess formation in which he demonstrated pure cultures of influenza bacilli eight times during a period of five weeks. When the lung is extensively involved with an increasing amount of sputum and continued fever the case assumes a serious aspect. Every effort should be made to localize the process. The *x*-rays are a valuable adjunct to physical examination, and the involvement of the overlying pleura may indicate the site. In more favorable cases the abscess is walled off and the patient left with a cavity communicating with the neighboring bronchus, which may be dilated. The affected lung may contain numerous cavities. Pulmonary induration usually accompanies these changes.

Chronic Influenza.—It is not surprising that the acute attack should occasionally initiate a chronic cough. The losses of pulmonary tissue serve as permanent pockets for influenza bacilli. The writer has seen 3 cases in which influenza bacilli persist in the abundant purulent sputum two and one-half years after the acute attack. Leichtenstern followed 2 patients from the acute attack to their death two years later. No tuberculosis was found at autopsy. Chronic infection with influenza bacilli is a very frequent clinical finding. Eighteen such cases were reported by the writer in 1902. It is often impossible to establish the onset in an acute infection.

The cases may show only local or diffuse bronchitis on physical examination, yet some damage to the pulmonary tissue has probably always occurred. In other cases slight dulness or bronchovesicular breathing

may establish the site of the pulmonary process. In the more severe cases the symptoms are those of local or diffuse bronchiectasis. The sputum may reach an enormous quantity, sometimes amounting to a pint or more in twenty-four hours. Blood streaks or even frank hemoptysis may be present without tubercle bacilli in the sputum or a reaction to tuberculin. Such hemorrhages come from abscess cavities or congested veins in the walls of dilated bronchi. The cases closely simulate tuberculosis, but their course is more favorable. They do not tend toward a fatal termination, but rather remain stationary or slowly advance, unless acute bronchopneumonia arises from the chronic infection, or death results from some intercurrent disease. In one case the cough had lasted for forty-four years, and death followed cerebral hemorrhage. At autopsy, bronchiectasis, chronic interstitial pneumonia, and abscess formation have been found. Boggs[1] demonstrated influenza bacilli in the bronchial wall at autopsy in two cases of bronchiectasis.

Pneumothorax and Empyema.—If abscesses are present at the periphery of the lung, their rupture may lead to invasion of the pleural sac, resulting in fibrinous pleuritis, pneumothorax, or empyema. The exudate may contain influenza bacilli alone, but mixed infections are more common. Empyema was present in 6 of Mason's 77 cases of influenza pneumonia.

Lobar Pneumonia and Influenza.—Many writers think that lobar as well as bronchopneumonia should be regarded as a manifestation of influenza. No convincing arguments as yet support this view. The writer has repeatedly sought influenza bacilli in the exudate of lobar pneumonia, and in typical cases has never demonstrated them in stained sections. The clinical distinction between the two forms may be impossible, and the croupous pneumonia complicating influenza may run a very atypical course.

Relapse.—Some patients who have once suffered from influenza seem to be especially liable to recurrences; which may be due to the persistence of the bacilli, undetected, in the upper parts of the respiratory tract, causing auto-reinfection. They may persist for years in some cases. Relapse is more frequent in the colder months of the year, but may immediately follow the original attack after some indiscretion, especially exposure to cold. It is usually less severe than the first infection.

2. **Nervous.**—It has been said that the clinical picture of influenza is incomplete without nervous phenomena. This is probably true, in previously uninfected individuals, if we include the minor nervous disturbances. Headache and general pains are seldom absent in acute cases. Prostration is frequent and often far outlasts the symptoms of the disease. Vertigo, insomnia, even delirium and coma, may occasionally be observed. The nervous symptoms may so far predominate that local respiratory changes are overlooked. In some cases, to judge from the literature, nervous disturbances may be the only manifestation. In such cases, however, it is difficult to exclude diseases which have no relation with influenza. Neuralgic pain is one of the most common

[1] *American Journal of the Medical Sciences*, 1905, cxxx, p. 902.

disturbances. It usually occurs after the decline of the fever and may last long into convalescence. Hardly a nerve in the body has escaped a relation with influenza. Peripheral neuritis, paralysis of various eye muscles, hemorrhagic myelitis, and epilepsy have been observed. Among the German army cases persistent nerve pain was noted in 254 (0.46 per cent.). Various other nervous disturbances may accompany or follow influenza. Their relation with the disease is somewhat uncertain because of their rarity. Psychoses may follow influenza as they do typhoid fever or ordinary pneumonia. The prognosis is favorable in cases dependent on influenza and without predisposition to the disease. Patients have been admitted to insane asylums and discharged well after a few weeks, but more severe cases may not recover for months.

Encephalitis may arise apparently by extension from the middle ears, the nasal or frontal sinuses, and the antrum of Highmore; from metastasis in pulmonary abscess, empyema, or purulent bronchitis; or it may be impossible to find a primary source. Monoplegia, hemiplegia, coma, convulsions, or delirium, may result. Leichtenstern was the first to describe such cases, and Pfuhl claims to have found influenza bacilli in cerebral tissue.

Meningitis.—This must be regarded as a very rare manifestation of influenza, occurring in only four of the German army cases. Toxemia has been said at times to simulate meningitis, but it must always be a question without lumbar puncture whether a true infection has not been present and followed a very favorable course.

Influenza meningitis is more frequent in infancy and childhood than in adult life. It is practically always secondary to disease of the respiratory tract or its adnexa through the blood stream or by direct extension. Fifty-eight cases have been reported in which the influenza bacillus was demonstrated in the exudate; only six recovered.

The cases closely resemble meningitis due to the pneumococcus or meningococcus. Their influenzal origin may be suspected during an epidemic or when some primary focus of influenza can be demonstrated. Even then without lumbar puncture, their bacterial cause remains uncertain. From their more sudden onset and more rapid course the clinical distinction between influenza and tuberculous meningitis can often be made. The pathological picture of influenza meningitis is not characteristic.

3. **Gastro-intestinal.**—This form of influenza as an entity is of uncertain existence. The symptoms referred to this tract may be toxic phenomena secondary to the respiratory or nervous form. On the other hand, in the German Collective Investigation 39 cards deal with this point and only 1 denies the possibility of separating the different forms, while 38 affirm the distinction. It is to be hoped that in recurring epidemics the specific cause of the disease will be demonstrated in the lesions or that cases with exclusive gastro-intestinal symptoms will be shown to be more frequent than before or after the epidemic period. Until this can be done we must rely on the impression of medical men for the establishment of the group. The writer has never seen a case

with absence of respiratory symptoms in which the diagnosis was sure. Heyrooski obtained a pure culture of influenza bacilli from the pus of a case of cholecystitis and cholelithiasis. The identification of the organism was complete.

4. **Typhoid Form of Influenza.**—Cases with fever, headache, delirium, meteorism, and diarrhœa may at first suggest typhoid fever. Rose spots have even been described. A palpable spleen has been noted in as high as 12 per cent. of cases by Schultz, while it occurred in only 4.7 per cent. of Krehl's cases. Continued fever with only transient local manifestations may follow infection with influenza bacilli. The writer has frequently found influenza bacilli in the sputum of patients with continued fever who gave positive Widal reactions, showing that the two infections may coexist; and it is not certain that the so-called typhoid form of influenza is not unrecognized typhoid fever. Jaundice probably bears only a chance relation with influenza. Parotitis has been occasionally observed. It occurred in 12 of the German army cases.

5. **Circulatory System.**—Functional cardiac disturbances are not uncommon, but are not distinctive and are such as may occur in any acute infectious disease. The pulse-rate is usually elevated in proportion to the fever, but in some cases tachycardia may be noted. Bradycardia, palpitation, irregularity, and dicrotic pulse may be occasionally seen.

Endocarditis.—Influenza is so seldom followed by permanent cardiac disturbances that it is not usually held responsible for valvular disease. It seems probable, however, that it is not as blameless as is commonly believed. More recent observations on the bacteriology of the disease show that influenza bacilli not infrequently invade the blood-stream, especially in severe attacks. Their lodgement on the cardiac valves has been established among others by Jehle,[1] Horder,[2] and F. J. Smith.[3] Pericarditis may arise by extension when the lung or pleura have become involved. Influenza bacilli, mixed with other organisms, have been found in the exudate.

Disturbance in the peripheral vessels—phlebitis, venous and arterial thrombosis—may occur, as might be expected from the infectious nature of the disease.

Septicemia.—Numerous observers have described organisms resembling influenza bacilli in the blood of patients with influenza. Blood cultures and the search for influenza bacilli should be more systematically made in acute febrile infections of obscure origin. Madison[4] was able to collect 30 cases in which the influenza bacillus had been cultivated from the blood during life. They have been found in the heart's blood after death by Rosenthal, Doering, and Jehle. Jehle's work is of special interest. His observations were all at the postmortem table. Of 20 cases with pulmonary influenza the bacilli were found in the blood in

[1] *Zeit. f. Heilk*, 1901, xxii, 3 abt., 190.
[2] *Lancet*, 1905, ii, 1473.
[3] *Ibid.*, 1908, p. 1201.
[4] *American Journal of the Medical Sciences*, 1910, cxxxix, 527.

only 3. In the acute exanthems, on the contrary, an invasion of the blood by influenza bacilli was almost the rule.

The Blood.—We have made leukocyte counts on 233 cases of influenza at the Massachusetts General Hospital. Of these 167 represent the simple and typical form of the disease, with an acute onset, usually with fever of short duration, and in most cases slight respiratory disturbance. The leukocytes do not exceed 12,000 in about 70 per cent. The leukocytosis in the remaining cases cannot be ascribed to complications, nor is there any relation between the white count and the severity of the infection. With the involvement of the deeper part of the respiratory tract the proportion of cases with leukocytosis increases, as only about one-half of 54 cases with bronchitis, and only one-third of 12 cases with pneumonia show 12,000 leukocytes or under.

6. **Genito-urinary.**—Beyond the slight disturbance in the kidney commonly found in any acute infectious disease, there is nothing particularly noteworthy in influenza, which seems to spare this organ in the vast majority of cases. In very rare instances a nephritis has been noted, as in 10 of the German army cases. The finding of influenza bacilli in the kidney at autopsy has been reported by Paltauf and Kretz, and J. H. Wright demonstrated them in a case of pyonephritis. Cystitis and orchitis have been described. Abortion following an attack of influenza has been frequently noted, especially by the older writers.

7. **Skin.**—Herpes of the lips and nose was noted in 5 per cent. of Leichtenstern's 105 cases of pneumonia and in 3 per cent. of 334 uncomplicated cases. Erythema, scarlatinal, measly, and other exanthems have been ascribed to influenza; but they are not distinctive and occur so infrequently as to suggest a drug rash or confusion with other diseases.

8. **Joints.**—No special relation has been established between arthritis and influenza. Dudgeon and Adams[1] found the influenza bacillus in pus obtained from the elbow- and hip-joints. "Acute articular rheumatism" was observed in 44 of the German army cases.

9. **Special Senses.**—*Ear.*—The relation between influenza and inflammation of the middle ear is undoubted. Though otitis media was noted in only a small proportion of the series of cases reported from the last pandemic, slight catarrhal inflammation is common, and it was generally observed by ear specialists during the outbreak that the number of cases seeking admission far exceeded those before and after the epidemic. Gruber,[2] for example, saw 324 cases of otitis media (138 catarrhal—186 purulent) during the month of January, 1890, while his monthly average for January at other times was 58 cases.

Involvement of the mastoid and invasion of the meninges may occur. Otitis media should always be suspected in children with severe obscure symptoms. Perforation of the membrana tympani may be the first objective sign. Influenza bacilli have been frequently demonstrated in the middle ear, but usually mixed with other bacteria.

Eye.—Conjunctivitis may be noted in a variable proportion of cases. It was observed in as high as 40 per cent. of Stinzing's 405 patients.[3]

[1] *Lancet*, 1907, ii, 684. [2] Gruber, *Wiener med. Woch.*, 1890, No. 10.
[3] Stinzing, *Münch. med. Woch.*, 1890, No. 93.

The process is usually benign, and no marked increase of the number of those seeking admission to the eye clinic was noted during the epidemic. In the more severe cases the conjunctivitis is accompanied by photophobia and œdema of the lids. The bulbar conjunctiva may be involved and corneal ulceration may result. Iritis and iridocyclitis have been described. Influenza bacilli have been found in the conjunctival secretion.

Influenza and Other Diseases.—Though it has often been thought that during epidemics of influenza other diseases do not prevail to the same extent, the reports are conflicting, and it may be that during the outbreak of influenza other diseases are at times wrongly included under its manifestations. The unfavorable influence of influenza on existing disease, however, is undoubted. Superimposed on phthisis, emphysema, cardiac disease, nephritis, or diabetes, it may lead to a fatal termination. Jehle found that during a small local outbreak both the morbidity and mortality of scarlet fever were increased.

Phthisis.—The effect of influenza on phthisis is difficult to estimate in isolated cases, but is shown by hospital and mortality statistics. Sixty-seven cases were discharged because of phthisis, from service in the garrison in Munich during the year preceding the 30th of September, 1889; but within the next six months, during the epidemic of influenza, 132 cases were discovered. The diagnosis was based on the finding of tubercle bacilli in the sputum. The vital statistics for Paris show that 349 persons were reported as having died from phthisis between December 22, 1888, and January 4, 1889, while 886 deaths are recorded from the same cause during an equal period in 1889–90. Following the epidemic it was observed that the number of deaths from tuberculosis fell below normal, suggesting that influenza had merely hastened the fatal termination. In some cases influenza pneumonia may complicate phthisis without apparently exerting an unfavorable influence.

Diagnosis.—Clinical.—During epidemics and pandemics this presents little difficulty in cases beginning suddenly with chills, fever of short duration, headache, general pain, loss of appetite, and prostration out of proportion to the other symptoms. The patient may complain of no local lesion, but catarrhal disturbances are almost the rule. They may be transient and easily overlooked in the predominance of nervous and gastro-intestinal symptoms. The protean character of the disease makes it difficult to separate its rarer manifestations from diseases of a different etiology occurring during epidemics.

Bacteriological.—Influenza bacilli can be recognized after some practice from their morphology and staining reaction alone in most cases. To be certain of their identity, however, they must be cultivated.

Other Catarrhal Respiratory Infections.—In the interepidemic period it does not seem that the respiratory infections with influenza bacilli can be distinguished from infections with other organisms, such, for example, as the *Micrococcus catarrhalis*, without a bacteriological examination of the sputum. In the clinical picture, symptoms of onset, the course and duration of the different infections, there seems to be nothing distinctive. The prostration may be as great in one as in the other.

Tuberculosis.—Infection of the lungs with influenza bacilli may closely simulate pulmonary tuberculosis. The persistence of rales at some place in the lung may be due to small losses of substance during an undetected influenza bronchopneumonia. Signs of cavity or long-continued pulmonary solidification may result from infection with other organisms than the tubercle bacillus. It is by no means rare to see patients in whom the suspicion is strong that the disease is pulmonary tuberculosis, from the long-continued cough, occasional attacks of hemoptysis, and suspicious physical signs; but repeated examination of the sputum fails to reveal tubercle bacilli and no reaction is obtained after the injection of tuberculin. The writer has reported eight cases[1] from the Massachusetts General Hospital in which the confusion might readily have occurred or in which the clinical diagnosis of pulmonary tuberculosis had been made, but without tuberculosis at autopsy. If a history of preceding catarrhal symptoms or an onset with an acute febrile attack can be obtained, influenza should be suspected. Hemoptysis occurring without catarrhal symptoms is likely to be due to tuberculosis; but in the presence of serious damage to the pulmonary tissue it may come from abscess cavities of a non-tuberculous origin.

The early detection of pulmonary tuberculosis is so important that it is usually safer to give the patient the benefit of the doubt and treat him for tuberculosis; but in view of the impossibility of making the diagnosis without finding tubercle bacilli in the sputum, their presence should be regarded as the only infallible indication of this condition. In their clinical course the influenza infections are more favorable than tuberculosis, tending rather to remain stationary or slowly advance, unless fatal from some intercurrent disease. Influenza has been frequently confused with dengue and mild cases of typhoid fever.

Prognosis.—Few die compared with the number attacked. Many statistics are untrustworthy because some of the more serious manifestations are not included. Influenza becomes more dangerous with advancing years or in patients with phthisis, cardiac disease, emphysema, diabetes, etc. Of the 55,263 German army cases, only 59 died from influenza—42 with pulmonary symptoms. Of 22,972 cases in Munich, death was ascribed to influenza in 133, of whom 69 died of pulmonary disturbance. Influenza pneumonia is more serious than lobar pneumonia. Various estimates place the mortality at from 17 to 50 per cent. It is to be feared not only from its high mortality, but also because of its distressing sequelæ arising from occasional permanent damage to the pulmonary substance. Continued cough, recurring respiratory infection, chronic bronchitis, emphysema, pulmonary induration, and bronchiectasis, add to the seriousness of this manifestation of the disease. Influenza meningitis is a very fatal form.

Prophylaxis.—The contagious nature of influenza seems to have been conclusively proved. The secretion from the respiratory tract must be regarded as the principal source. Contact infection and the drying of sputum should be guarded against.

[1] Lord, *loc. cit.*

The most important preventive measures concern the elimination of recurring epidemics. If the influenza bacillus is the cause it maintains its existence by numberless interepidemic infections and by its persistence for years in the respiratory tract of individuals with chronic cough. In unselected cases the writer has found the organism present in from 25 to 59 per cent. of all cases with cough and expectoration in an interepidemic period. It is to these cases of acute and chronic respiratory infection occurring outside of epidemics that preventive measures must be directed. The same control should be exercised over all cases of respiratory infection as is now attempted for tuberculosis. Influenza should be considered as constant a danger as tuberculosis, though its manifestations are less serious. All patients with cough and expectoration coming to polyclinics or seen in private practice should be warned against the danger of transferring infectious material from person to person, with the same care as in tuberculosis.

During epidemics persons at the extremes of age should be protected with special care. When possible isolation should be practised. Infected boats should not land passengers at uninfected ports. Mass meetings should be discouraged. Infected children should be kept from school.

Tuberculous patients should be guarded at all times from influenza infection. On the other hand the admission of unproved cases to institutions for the cure of tuberculosis subjects them to an unnecessary danger. If they are admitted on suspicion of tuberculosis they should be placed in separate wards until they can be proved to be tuberculous. The damaged condition of their bronchi and lungs renders them more susceptible to the tubercle bacillus.

The safest method of disposal of sputum is cremation. The most efficient of the ordinary solutions is probably carbolic acid (5 per cent.), which may be left in contact with the sputum for twenty-four hours.

Patients who continually harbor the influenza bacillus in some part of the respiratory tract should be especially careful to avoid exposure to wet and cold. Catarrhal symptoms so frequently follow such indiscretion that something more than a chance relation must exist between exposure and acute respiratory infection or reinfection. The experiments of Rossbach and Müller on animals have shown that the chilling of the body is followed by a transitory increase of bronchial secretion, which may serve as a favorable medium for the multiplication of organisms in an already infected tract. Some protection may be afforded by efforts at increasing individual resistance—sleeping with the window open, spending much time in the open air, and cool morning baths followed by friction. A good reaction should be secured after the bath. The hardening process should not be begun during cold weather.

Treatment.—There is no specific for influenza. In the great majority of cases the disease runs its course independent of treatment. The diet should be regulated and should be light and easily digestible in cases with gastro-intestinal symptoms. With involvement of the respiratory and nervous systems there are no special restrictions, and the patient may take as much food as can be easily digested.

Even the mild cases should be regarded as serious, and the patient

confined to the house and the bed, remaining there until the acute symptoms and fever have subsided. At the onset the patient may take a hot bath and be put to bed between warmed blankets with hot-water bottles at the feet. A drink of hot lemonade may serve to start perspiration, which is often followed by surprising relief of the headache and general pains. An increase of respiratory symptoms may follow chilling the body, and cold should be limited to local applications for pain.

If the headache and general pains are distressing an ice-cap and Dover's powder, gr. 10 (0.65 gm.), may be ordered. If the bowels have not moved, a mild saline cathartic, as sodium phosphate, 30 gr. (2 gm.) in half a tumbler of lukewarm water, may be given. The coal-tar products must be used with caution, but if the headache, general pains, hyperesthesia, or insomnia, are marked, antipyrine or phenacetine, gr. 10 (0.65 gm.), with caffeine, gr. 3 (0.2 gm.), may give evident relief. They are of service also in the severe neuralgic pains following influenza. Their use must not be long continued. When facial neuralgia persists, disease of the nasal sinuses should be suspected. The bromides, nitroglycerin, salicylic acid, aspirin, etc., may be given a trial. Locally, chloral and camphor, chloroform liniment, menthol, etc., may be of service. In lumbago, sacro-iliac disease should be suspected. In sciatica the thermocautery or electricity may be tried.

If the patient is harassed by irritative attacks of cough, heroin, gr. $\frac{1}{12}$ (0.005 gm.), or morphine may be used. If the secretion is raised with difficulty, ammonium chloride, gr. 10 (0.65 gm.), often seems to be of great service. If the cough persists, tubercle bacilli should be repeatedly looked for in the sputum. A change of surroundings and life in the open air may accomplish more than any other method of treatment. The testimony of patient with chronic bronchitis, bronchiectasis, and emphysema is practically unanimous that they are better during the warm months of the year. They undoubtedly do better leading an outdoor life in a warm equable climate and in an atmosphere free from dust.

A tight thoracic binder will often relieve the pleuritic pain accompanying influenza pneumonia. The ice-bag is usually more efficient. If relief does not soon follow, or if the cough or dyspnœa is distressing, morphine should be used. With anomalous signs of pulmonary solidification, exploratory puncture should not be delayed.

The physician should always have otitis media in mind in children with severe obscure symptoms. With predominance of nervous phenomena, meningitis should be suspected; if present, lumbar puncture may afford temporary relief of symptoms. Wollstein was able to produce an immune goat serum capable, when injected into the subdural space, of bringing about recovery in monkeys with experimental influenza meningitis. This should be tried in human influenza meningitis.

The convalescence should be carefully managed. A relapse may follow the too early resumption of customary duties. It may be weeks or months before complete health returns. Fresh air, nutritious food, and tonics may hasten recovery.

CHAPTER IX

TOXEMIA, SEPTICEMIA, AND PYEMIA

By RICHARD M. PEARCE, M.D.
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Introduction.—A consideration of toxemia,[1] septicemia, and pyemia is necessarily a discussion of infection and its sequelæ.

An *infection* is the condition produced by the entrance and growth within the body of pathogenic microörganisms. An infection may be local or general.

Toxemia.—In a local infection the organisms multiply at the point of invasion, and cause, through the toxic substances which they elaborate, local tissue changes. At the same time these toxic substances pass into the general circulation and produce certain constitutional symptoms. This secondary condition is best described by the term *toxemia*. Such is the usual course of events in certain of the acute infectious diseases, as diphtheria. In some diseases, as tetanus, no demonstrable tissue changes occur at the site of inoculation, all symptoms being due to the intoxication resulting from the absorption of the bacterial products.

Although it is possible that substances elaborated in the destruction of tissue may cause an intoxication independent of bacterial action, we have little positive evidence that this is a common occurrence. It would seem advisable therefore to drop the old term *sapremia* in favor of toxemia. The term sapremia, first applied to the group of symptoms supposed to be caused by the absorption of the products of decomposition, and used almost exclusively in a surgical sense, does not accurately characterize the general group of intoxications due to bacterial products and of interest now to the physician as well as to the surgeon.

Bacterial intoxication, however, may occur in the absence of infection, for example, in the various forms of food poisoning. Under these circumstances the symptoms due to a poison introduced in large amount into the gastro-intestinal canal depend only upon the rapidity and amount of absorption; infection does not occur, for the organism which produced the toxic substance, even if present, does not invade the tissues. It is essential therefore in considering bacterial intoxications to distinguish between those following infection and preceded by a period of incubation and those due to the absorption of preformed toxins without infection. The latter comprise those due to food poisoning and those due to the action of the putrefactive flora of the intestinal tract. Certain headaches, neuralgias, anemias, and even some types of

[1] The term toxemia is used here to include only those forms of intoxication due to the products of bacteria; other forms due to altered metabolism, as, for example, the toxemia of pregnancy and the various cachexias, do not come within the scope of this section.

pernicious anemia would seem to be due to toxic substances of intestinal origin usually associated with an intestinal flora in which putrefactive bacteria predominate.

Septicemia.—The older conception of septicemia as a surgical affection, due to the invasion of the blood by the organisms of suppuration, has delayed the acceptance of the term in its broader meaning. The general invasion of the blood and tissues by any of the pathogenic bacteria constitutes a septicemia, and it matters not whether the general infection follows local suppuration, or is a part of some disease as gonorrhœa or pneumonia, or even develops without evident portal of entry. Most of the acute infectious diseases, such as typhoid fever, pneumonia, epidemic meningitis, influenza, etc., belong to this group. The application of the term *bacteriemia* to this condition is an attempt to avoid the older terminology. The constitutional symptoms of a septicemia are naturally those of toxemia and due to the same factor, *i. e.*, the poison elaborated by the infecting organism. There is, however, this difference: In toxemia the poison is formed at the local focus and absorbed therefrom, while in septicemia it may also be formed in all parts of the body. In the former the symptoms usually disappear with the removal of the local infection, while in the latter such removal, once the process is well established, has less effect.

Pyemia.—When, in the course of a general invasion of the blood and tissues by a pathogenic microörganism, multiple secondary foci of suppuration appear, the condition becomes a pyemia. These secondary foci include abscess, diffuse suppuration, endocarditis, synovitis, or any other inflammatory condition of either the solid structures or the body cavities. The term pyemia therefore includes more than the mere development of secondary abscesses. For example, a gonococcus septicemia accompanied by an ulcerative endocarditis and suppuration in the joints, due to the same organism as a result of its dissemination in the blood is, strictly speaking, a pyemia, although abscesses in the ordinary sense may not be present.

While in the majority of pyemias the secondary lesions are due either to the streptococcus or the *Staphylococcus pyogenes aureus*, other organisms as the pneumococcus, the gonococcus, and the colon and typhoid bacilli, may produce suppuration. The distribution of the infecting organism may at times be accomplished by fragments of thrombi, which, becoming separated from the local lesions, pass as emboli to various parts of the body and, if conditions are favorable, cause suppuration wherever they lodge. Pyemia obviously includes both septicemia and toxemia.

Historical.—Previous to the development of bacteriology the theories concerning wound suppuration and its complications were naturally based on anatomical observations. Pyemia therefore received early attention, while the explanation of septicemia and toxemia was delayed until the advent of bacteriology.[1]

[1] For good historical reviews see W. Watson Cheyne, "Suppuration and Septic Diseases," Edinburgh and London, 1889; ibid., "Septicemia and Pyemia," Allbutt's *System of Medicine*, 1896, i, 586; also v. Kahlden, "Sepsis," Eulenberg's *Real Encyclopädie der gesammten Heilkunde*, 1899, xxii, 329.

The first attempt to explain the secondary abscesses was made by Boerhaave, who, in 1720, affirmed that these were due to a contamination of the blood by the pus of the wound. In 1774 John Hunter demonstrated the association of suppurative phlebitis and pyemia. The recognition of a general toxic condition independent of the local suppuration of pyemia was largely due to the work of D'Arcet (1842), who asserted that in septic infections two associated but distinct processes exist, a general poisoning due to the absorption of putrid products and a plugging of the vessels by emboli. The first explained the fever and constitutional symptoms, the second, the metastatic abscesses. Virchow demonstrated later that the general septic condition could occur without metastatic abscesses; thus he distinguished between toxemia or septicemia and pyemia as we now use the terms. The experiments in support of this view were made with putrid pus. It was found that well-filtered pus caused only the constitutional symptoms, while unfiltered pus, containing small masses of cells, led to the formation of embolic abscesses.

Meanwhile, early in the nineteenth century, several investigators had studied experimentally the effect of injecting infusions of putrid meat and other substances. These and other investigations which followed, although they led eventually to the discovery of ptomains and to the elucidation of the various forms of food poisoning, aided in the solution of the problems of septicemia only by the impetus they gave to the study of bacterial products. A little later the rapid advance of bacteriology allowed the application of methods which soon demonstrated the true nature of wound infection and its sequelæ—toxemia, septicemia, and pyemia—and eventually to Lister's statement of the principles of antisepsis.

To Koch, especially, is due the credit of experimentally distinguishing between septic intoxication and true septicemia and the relation of pyemia to the latter. He was able to demonstrate the rapid toxic action of large doses of putrid fluids with fatal result within a few hours; and with small doses, 1 to 2 minims in mice, a gradual onset of symptoms, which developed in about twenty-four hours and usually resulted fatally. The blood of the latter animals contained bacteria which he was able to cultivate. With minute amounts of these cultures he reproduced the disease, thus demonstrating that septicemia was a true general infection differing from putrid intoxication in which he found no organisms in the blood. He also demonstrated, in a micrococcus septicemia, a plugging of the vessels by emboli composed of colonies of cocci and adherent red blood corpuscles, a condition somewhat analogous to the closure of vessels by embolic portions of infected thrombi.

Etiology.—Toxemia.—Under this term may be included all intoxications due to the absorption of bacterial poisons. As stated previously, these may be classified into two subdivisions: (1) The toxemias due to bacterial action outside the body tissues, including food poisoning, and the products of intestinal putrefaction; and (2) the toxemias arising from the action of bacteria upon the body tissues. The toxemias of the latter group when due to infected wounds or to suppurative processes, whether in one of the hollow viscera, in the sinuses, or in the tissues of the body, produce much the same pathological lesions and clinical

symptoms. On the other hand, the toxemias of this second group, associated with the acute infectious diseases, have to some extent individual peculiarities. Even here, however, except in the case of a few organisms, notably the tetanus bacillus, the systemic toxemia is much less specific than the character of the lesions at the foci of infection.

That the characteristic effects of a pathogenic microörganism are due to the chemical substances which it elaborates is now generally accepted. This may be manifest not only in the character of the local lesion, but also in the degree and nature of the constitutional disturbance. Thus in typhoid fever, cholera, diphtheria, and pneumonia, though each has a distinctive local lesion, widespread systemic disturbances occur; on the other hand, in gonorrhœa, except in peculiarly virulent infections, the action of the poison is confined to the place of its formation. Some organisms in addition to the production of a general toxin also produce a special poison as shown by the peculiar involvement of the peripheral nerves in diphtheria and the motor neurons in tetanus.

The substances resulting from bacterial activity may be conveniently grouped as ptomains and toxins. Vaughan and Novy[1] define a ptomain as "an organic chemical compound, basic in character, and formed by the action of bacteria on nitrogenous matter." These substances are also called putrefactive alkaloids. The ptomains are to be regarded as "extracellular products of bacterial activity. They do not originate within the bacterial cell, and therefore are not to be looked upon as direct metabolic products of the cell protoplasm, but rather as secondary cleavage products." They are formed almost exclusively outside the living body and therefore play but a small part in producing pathological conditions. When, however, they are ingested with food, they cause an acute, severe, and frequently fatal intoxication. Kaensche's researches show that at least three different bacilli may produce toxic substances in decomposing meat. Many of the ptomains resemble certain vegetable alkaloids in either their chemical or physiological reactions. Some may be obtained from a variety of decomposing substances, irrespective of the type of organisms present. Others appear to be associated with the growth of certain organisms, as cadaverin with the genus vibrio; tetanotoxin, spasmotoxin, and tetanin (Brieger) with the *B. tetani;* the poison of cheese (tyrotoxicon) with members of the colon group (Vaughan) and pyocyanin with the *B. pyocyaneus.*

The toxins, unlike the ptomains, are the result of synthetical processes occurring within the bacterial cell. They are all, probably, proteid substances and may be divided into toxins, toxalbumins, and bacterioproteins. Toxins and toxalbumins are soluble, the former of unknown chemical composition, the latter partaking of the chemical nature of albumins. The bacterioproteins are the proteid elements of the bacterial cell. Here, however, the term toxin will be used in a general way to indicate the toxic products of bacteria without regard to their chemistry or their power to stimulate the formation of an antitoxin. It is customary to distinguish between extra- and intracellular toxins. By the former

[1] *Cellular Toxins or the Chemical Factors in the Causation of Disease,* 1902.

we mean those soluble chemical substances which are found in the filtrate of the fluid in which the bacilli have grown and which represent the result of synthetical processes in the cell. To this group belong expecially the toxins of the diphtheria and tetanus bacilli. Some organisms, however, yield a toxic substance only upon the disintegration of the bacterial cell. These are known as intracellular toxins or endotoxins, and to this group belong the majority. A distinction is sometimes made between specific and non-specific toxins. The tetanus toxin, for example, which is peculiar to the organism which generates it and has an affinity for the motor neurons, is said to be specific; while a toxin which is similar in nature and action to the products of a number of other organisms is non-specific. Most of the bacterial toxins are of the latter type.

Septicemia and Pyemia.—As pyemia depends on an antecedent septicemia, the etiology of these two conditions may be considered in common. A septicemia can develop only as the result of infection at some point, but the portal of infection is not always recognized. Thus in septicemias following wound infections, suppurative processes, tonsillitis, puerperal sepsis, diphtheria, or gonorrhœa, the focus of infection is readily recognized. In pneumonia, influenza, meningitis, typhoid fever, tuberculosis, and other diseases, the precise portal of entry is often obscure. Finally, there are cases of septicemia due to Streptococcus pyogenes and other organisms in which, in spite of the most careful search, no superficial involvement which might have been the point of infection can be discovered. The organisms which have been found in septicemias of unknown origin are, in order of the frequency of their occurrence: the streptococcus, the staphylococcus, the pneumococcus, the typhoid bacillus, the colon bacillus, *B. pyocyaneus*, Friedländer's bacillus, the meningococcus, the *Micrococcus tetragenus*, and a few others. A septicemia may be due to the organism causing the primary lesion, as a pneumococcemia in association with lobar pneumonia; or it may be due to a secondary invasion, as a streptococcemia in diphtheria.

Of supreme importance in the study of septicemia has been the determination of the organisms capable of producing a general infection. The early work concerning the relation of local suppuration to septicemia and pyemia contains many references to bacteriological examinations. In some instances this included only a determination of the organism in the local lesions, while in others an attempt was made to correlate the findings in the primary infection and in the secondary pyemic foci. Although this is of importance, as is also the data obtained by the routine bacteriological examination of the blood and organs at autopsy, the greatest progress has been made as the result of the examination of the blood during life.

An exhaustive consideration of the bacteriology of the septicemias, especially of those forms occurring in surgical and obstetrical practice, would be too bulky for the present discussion.[1] The relation of all the

[1] For the general literature of this subject see Kühnau, *Zeitschr. f. Hygiene u. Infektionsk.*, 1897, xxv, 492; Kahlden, *loc. cit.;* Rosenberger, *Proceedings of the Philadelphia Pathological Society*, 1903, vol. vi, 157.

above-named organisms to these has been definitely established. Cabot (1904) has summarized a score of the more important investigations covering conditions usually termed "septic" by the surgeon or obstetrician and including endocarditis and suppurative arthritis. He finds a total of 316 examinations with positive results in 107, or 33 per cent.

The bacteriemias occurring in medical practice, however, deserve special consideration. A clinical rather than a bacteriological classification offers the best basis for discussing these.

Pneumonia.—That a pneumococcemia, analogous to the similar condition produced in animals experimentally may occur quite constantly has been demonstrated in a very extensive series of investigations of the blood. Ewing in 1902 summarized twelve of the more important studies. These gave a total of 348 cases, in 160 of which the pneumococcus was isolated from the blood. Of these 160 cases, 64 ended fatally; while of the 188 in which the blood cultures were sterile, 37 died. Simon states that blood cultures give positive results in 50 per cent. of the fatal cases. Boulay considers the organisms isolated but a few hours before death to be the result of antemortem (agonal) invasion. Prochaska, who found the pneumococcus in all of 50 cases examined, believes the invasion to be a constant condition in pneumonia, as does Rosenow, who obtained positive results in 77 of 83 cases in which the blood was taken at all stages of the disease. Pearce, in a study of 118 cases of lobar pneumonia at autopsy, found the pneumococcus in the heart's blood, liver, spleen, or kidney in a little less than one-half of the cases.

Pneumococcemia without distinct localization has been reported by Wright and Stokes, Pearce, Flexner, Hektoen, and others. This is not an unusual form of terminal infection. In connection with bronchopneumonia, general infection with the pneumococcus, the streptococcus, the *Staphylococcus pyogenes aureus*, Friedländer's bacillus, or *B. typhosus* may occur.

Influenza.—Pfeiffer has found the *B. influenzæ* in the spleen, and Canon in the blood, of persons with influenza; while Jehle had found it in the blood in various of the acute infectious diseases of children (diphtheria, scarlet fever, measles, and varicella). M. Austin describes three cases of endocarditis in which a bacillus resembling that of influenza was found in films prepared from the vegetations; it was not obtained in cultures. That in these cases a true septicemia existed is supported by the investigation of Slawyk and Pfuhl. On the other hand, Pfeiffer and Kruse deny the identity of some of the organisms isolated by others, and Kühnau reports negative results in twelve cases.

Diphtheria.—The diphtheria bacillus for a time was supposed to cause a pure toxemia without systemic bacterial invasion. Frosch, in 1893, first demonstrated the escape of the bacilli into the blood and tissues, and his observations were quickly confirmed by Wright, Kanthack and Stephens, Nowak, Pearce, and others. Councilman, Mallory, and Pearce, in a study of 220 fatal cases of diphtheria, found the diphtheria bacillus in the blood or internal organs in 36 of 59 cases of diphtheria complicated by scarlet fever or measles, and in 83 of 161 cases of diphtheria only. In but a small proportion did it occur in pure culture.

The associated organisms were the streptococcus, the *Staphylococcus pyogenes aureus,* and the pneumococcus. All investigators agree that the most frequent form of general infection in diphtheria is streptococcemia. The possibility of the *B. diphtheriæ* producing pyemia is suggested by Howard's case of endocarditis and a few other instances of secondary suppuration due to this organism. The pyemia of diphtheria is, however, as a rule due to secondary infection by cocci.

Scarlet Fever.—So constant is the presence of the streptococcus in scarlet fever that some investigators believe it to be the cause of the disease. While, however, definite evidence of an etiological relation is lacking, it is found to be the most frequent form of general infection, and the cause of the great majority of secondary inflammatory complications. For example, in fatal cases Babes found it in the blood or internal organs in 17 cases, Pearce in 11 of 23 cases, Baginsky and Sommerfeld in all of 82 cases, Slawyk in 45 of 98 cases. The isolation of the streptococcus from the blood during life has been thoroughly studied by Hektoen, who gives also the most satisfactory opinion concerning the streptococcemia of scarlet fever. Although most observers have had indifferent success in cultivating the organism from the blood, Hektoen obtained positive results in 15 of 100 cases. Our present attitude concerning the streptococcus and scarlet fever may best be expressed in Hektoen's conclusions:

"The conclusions that suggest themselves from this work so far as scarlatinal streptococcemia is concerned are that streptococci occasionally may be found in the blood of cases of scarlet fever that run a short, mild, and uncomplicated clinical course; that streptococci occur with relatively greater frequency in the more severe and protracted cases of scarlet fever in which there also may develop local complications and clinical signs of general infection, such as joint inflammations, but even in the grave cases of this kind spontaneous recovery may take place; and finally, that streptococcemia may not be demonstrable in fatal cases of scarlet fever. The theory that scarlet fever is a streptococcus disease does not seem to receive any direct support from this work."

Smallpox.—To this disease the streptococcus bears the same relation as it does to scarlet fever. It is the usual cause of the secondary inflammatory complications and very commonly of a general infection. Ewing found the streptococcus in the heart blood of all of 29 cases of smallpox; while Perkins and Pay cultivated it from the various organs in 38 of 40 fatal cases and from the blood in 11 of 20 cases during life or shortly after death.

Gonorrhœa.—While in the vast majority of cases gonorrhœa remains a disease of mucous membranes, we find occasionally a true gonococcemia. These cases are usually pyemic in a strict sense, as they exhibit secondary inflammatory lesions, as endocarditis, phlebitis, synovitis or arthritis. The most complete study of this condition has been made by Thayer, who, working with Blumer (1895), first demonstrated the relation of the gonococcus to endocarditis and cultivated the organism from the blood during life; later with Lazear, he reported a second case. To these Lartigau, in 1901, added another, and four other cases are

noted by Rosenberger (1903), while not a few cases have recently been reported by French and German investigators.

Typhoid Fever and Paratyphoid Infection.—Previous to the observations of Kühnau, in 1897, typhoid fever was supposed to be a true toxemia, but he, by diluting the blood with large quantities of bouillon and making many plates, was able to obtain the organism from 11 of 41 cases examined. The collected cases now indicate that in typhoid fever a bacillemia exists in at least four-fifths of the cases. Corroborative evidence of the frequency of this condition is shown by the fact that bacilli are found in the rose spots in about the same proportion.

Of special interest are those cases of typhoid septicemia in which no intestinal lesions exist. Such cases present a typical clinical history, a positive Widal reaction, and the bacilli may be cultivated from the blood. The importance of this condition was first emphasized by Chiari and Kraus, and later in this country, by Flexner. In these cases special local lesions may occur in other organs than the intestine, as the lung or cerebral meninges. Such localizations are probably to be considered as secondary to the septicemia, and therefore pyemic in character.

Through the application of more exact bacteriological methods, the use of special media and of comparative agglutinative tests we now recognize bacteria resembling the *B. typhosus*, and causing a clinical picture similar to that of typhoid fever known as "paratyphoid fever." In many instances these organisms have been isolated from the blood.

Post-typhoid septicemia and pyemia are usually due to a secondary invasion of pyogenic cocci, especially the streptococcus, the staphylococcus, and the pneumococcus. The secondary suppuration may occasionally be due to the typhoid bacillus, but the damage is usually caused by cocci.

Tuberculosis.—While our knowledge of the dissemination of tuberculosis within the body affords evidence of the occasional escape of a few bacilli from the local lesions into the blood, it is in the acute miliary form of the disease that we have a true septicemia. Indeed, in this disease with its local lesion a bacteriemia, and a secondary eruption of tubercles, we have the same infection-mechanism as in ordinary pyemia; the only difference lies in the histology of the lesions, one being, as a rule, a proliferative, the other an exudative process.

Of great importance, from the clinical point of view, are the various forms of mixed infection which may occur in the late stages of the disease, especially in pulmonary tuberculosis with extensive ulceration. The toxemia or bacteriemia thus produced may cause exceedingly confusing symptoms. The organisms most frequently found are the *Streptococcus pyogenes*, *Staphylococcus pyogenes aureus*, *Diplococcus pneumoniæ*, and the pneumobacillus and allied capsulated organisms.

Anthrax.—In man the local lesion, malignant pustule, if not excised early, is practically always followed by a fatal septicemia. Under such circumstances the anthrax bacillus may occasionally be demonstrated in blood films or in cultures from the blood; a more satisfactory method, however, is the inoculation of an animal with the blood.

Bubonic Plague.—Bacillemia occurs, according to Atkinson, in about 80 per cent. of the cases. Ewing found the bacilli in 90 per cent. of the cases near death, and earlier in the disease in 60 per cent.

Bacillus Pyocyaneus Infections.—Under the term pyocyanic disease, or cyanopyemia, are grouped a variety of infections, usually local, occasionally general, due to the *B. pyocyaneus*. As a rule, the general infection has been demonstrated by bacteriological examinations after death, though Blum obtained the organism from the blood during life, and has demonstrated its relation to endocarditis.

Hemorrhagic Septicemia Due to Capsulated Bacilli.—Howard has described a type of septicemia characterized by hemorrhage into the skin, serous membranes, and various organs, in which capsulated bacilli (*Bacillus mucosus capsulatus* group) are found either alone or as the predominating organism of a mixed infection. Friedländer's bacillus, of this group, has been isolated from the blood during life, usually in cases of bacillemia associated with pneumonia, by Beco, Phillipi, and Boston. The occurrence of true pyemia due to Friedländer's bacillus has been emphasized by Etienne.

Rheumatic Fever.—The clinical picture of this affection closely resembles that of a septicemia, and the isolation of microörganisms offers support of such a view. Streptococci, staphylococci, and various bacilli, some of the colon type, and others anaërobic and bearing spores, have been found. The bacilli are found to have no constant relation to the disease, and opinion varies as regards the cocci. Beattie and others hold that the "*Micrococcus rheumaticus*" is distinct from the ordinary streptococcus and is the specific cause of the disease; in animals it causes articular and cardiac lesions and chorea. In this he supports the opinion of Poynton and Paine, Wassermann and Myer, and others. Singer considers the presence of the streptococcus to indicate that the disease is a streptococcic septicemia with pyemic manifestations.

Other organisms which have been obtained from the blood during life are the *B. mallei, B. leprœ, Diplococcus intracellularis meningitidis, B. aërogenes capsulatus, Micrococcus zymogenes*, and *Micrococcus tetragenus*.

Acute Endocarditis.—While a primary simple endocarditis is still recognized, it is probable that this, like the malignant form, is the result of a bacteriemia. The infection can be explained only by assuming that microörganisms reach the endocardium through the blood stream. Whether the infection results from an advanced septicemia or from a few stray organisms, the lesion of the valve affords a nidus favorable to the continuance of the general infection or capable of causing its exacerbation. We may conclude, therefore, that the presence of an organism in an endocarditis is evidence of its power to produce a septicemia, and that the endocarditis is a secondary focus of infection in this septicemia. The forms usually found are the streptococcus, the staphylococcus, the pneumococcus, and the gonococcus; occasionally the *B. typhosus, B. coli, B. diphtheriæ, B. tuberculosis, B. influenzæ, B. pyocyaneus*, and the meningococcus. Libman has recently demonstrated the existence of a group of acute endocarditis cases with rather characteristic cardiac and renal lesions often associated with arthritic lesions due to an organism

which he calls "*Micrococcus of endocarditis*," apparently closely related to the *Streptococcus viridans*.

There remains a group of diseases the infectious origin of which is not established, but which in many ways resemble mild, long-continued septicemias of low virulence; among these are certain cases of pernicious anemia, acute leukemia, some purpuras, and some of the subacute or chronic arthritides.

Terminal Infections.—This term is applied to those secondary infections which so frequently occur in incurable conditions, especially chronic diseases of the heart, liver, and kidneys, and are the immediate cause of death. Flexner has made an extensive study of such infections. In a series of 793 autopsies he found 255 cases of chronic heart or kidney disease, in 213 of which either a local or a general infection, or both existed; of these, 52 were examples of general infection. In some the point of entrance of the bacteria was evident, in others it could not be demonstrated. The organisms found were, in the order of their frequency, *Streptococcus pyogenes*, *Micrococcus lanceolatus*, the *Staphylococcus pyogenes aureus*, *B. aërogenes capsulatus*, *B. coli*, *Micrococcus gonorrhœæ*, *B. anthracis*, and *B. proteus*. Pearce in a study of pneumococcus infections found bronchopneumonia, frequently accompanied by a general pneumococcus infection, to be a common cause of death in chronic renal and cardiac disease; and less frequently in leukemia, general sarcomatosis and chronic tuberculosis. "It is perhaps safe to say that the majority of cases of advanced arteriosclerosis and of Bright's disease succumb to these intercurrent infections" (Osler). The same holds true for many other chronic diseases. Flexner, acting upon the supposition that the tendency to general infection was due to a diminished bactericidal power of the blood, carried out a series of investigations with the blood serum of persons suffering from advanced chronic diseases, and found it to be less destructive to the *Staphylococcus pyogenes aureus* than the serum of healthy individuals. More recently Longcope has demonstrated that a decrease in the bacteriolytic complement of the blood occurs in such cases.

The Value of Bacteriological Examination of the Blood.—It is evident from the preceding summary that the bacteriological examination of the blood during life gives results not only of scientific importance, but also of great value in diagnosis, prognosis, and treatment. Every clinician recognizes a group of diseases, with or without local lesions and etiologically independent, which present common symptoms characterized as "septic," *e. g.*, endocarditis and general miliary tuberculosis. These general symptoms may be due to toxemia, but in many a bacteriemia exists and an examination of the blood may establish an etiological diagnosis. For a rational use of serum or vaccine therapy such a diagnosis is essential, as has been emphasized by many investigators.

Concerning the usual forms of general infection in surgical practice, Ewing concludes as follows: "In the great majority of cases of local or general septic infections, septicopyemia, septicemia, pyemia, diffuse suppuration, osteomyelitis, etc., bacteria are present in the circulating blood *only for short periods and at infrequent intervals, most frequently*

during chills." That positive cultures may be obtained in many cases only following a chill or during an exacerbation of the fever has been repeatedly demonstrated. The importance of looking also for anaërobic organisms has been too generally neglected. Gwyn and Cole have isolated the *B. aërogenes capsulatus* from the blood during life. Burckhardt has recently, after failure with aërobic methods, isolated from the blood, in five cases of uterine sepsis, an anaërobic streptococcus which he calls *Streptococcus putridus.*

The Technique of the Bacteriological Examination of the Blood.—The following description, taken largely from Hektoen, covers all important points:

The best method to secure blood for bacteriological cultures is by venous puncture under the most scrupulous asepsis. Naturally, glass syringes are preferable to metallic because more easily sterilized and because transparent. The skin must be scrubbed carefully and prepared as customary for surgical operations. By some it is regarded as sufficiently cleansing to wash the area about the puncture with alcohol or ether. In practically all cases one of the veins at the elbow, usually the median, is selected for the puncture, and a moderate constriction of the arm will distend them so that in most persons they are made clearly visible and palpable. In fleshy persons it may be found impossible sometimes to make apparent in this way the location of veins, in which case it may be necessary to make the puncture more or less blindly. The discomfort is insignificant, and when properly done with a sterile needle, it is without danger.

Immediately on withdrawal of the needle after filling the syringe, suitable media should be inoculated with the blood before clotting takes place. In most cases it will probably be deemed most advantageous to inoculate small quantities of the blood, *e. g.*, 1 cc. into large quantities of some liquid medium like bouillon, *e. g.*, 100 cc. The main reason for this dilution is the necessity to overcome, as far as possible, the natural bactericidal properties of blood, at least for some bacteria. In order to increase the chances for positive results the number of flasks inoculated may be multiplied to almost any practicable number. Jacob believes that at least 20 cc. of blood should be taken in all cases, since in mild cases he has frequently obtained only from two to twenty colonies from this quantity. Gonococci and other organisms require special methods.

To obtain some idea of the number of bacteria in the blood it will be necessary to employ the plate method. This has been used with excellent results by Schottmüller in the study of typhoid fever. He has found that the mixing of 2 to 3 cc. of blood with 6 cc. of agar gives sufficient dilution. In the plates thus made the number of colonies developing may be counted and the bacterial content of the blood estimated.

During the process of inoculating flasks, or tubes of solid media, great care must be taken to prevent aërial contamination. The mouth of the uncorked flask should be held in such a way that bacteria cannot fall into the medium. It is to be remembered that one single coccus, for instance, is sufficient to cause contamination of a flask. The most

dangerous sources of contamination are the skin of the patient and the air. Undoubtedly organisms sometimes are picked up from the deeper layers of the skin as the needle passes through. In most instances the contaminating organisms will be found to be staphylococci, and it will be a safe rule to place no significance on the development of growths of staphylococci, especially other than *Staphylococcus pyogenes aureus*, in cultures from the blood, except under very special conditions. From time to time the finding of ordinary staphylococci in blood cultures has led to the misleading announcement that the cause of certain diseases of unknown etiology has been discovered.

The inoculated flasks are then placed in the incubator for twenty-four hours to six days, being examined daily for turbidity and other evidences of bacterial growth. When the bouillon remains sterile the blood corpuscles fall to the bottom intact, the supernatant fluid becoming clear, or nearly so. For *B. typhosus* and *paratyphosus* special media containing bile salts are desirable. For the pneumococcus, liquid media are especially valuable.

Pathology.—Toxemia and Septicemia.—With any given organism the general pathological picture is the same whether that organism produces a toxemia or a septicemia, for the lesions in either condition are due to the dissemination of the soluble chemical substances elaborated by the infecting microörganisms, and it matters little whether the latter remain in a localized lesion or circulate freely in the blood. It is therefore impossible to distinguish, except perhaps in degree, between the lesions due to septicemia and those due to toxemia. The character of these lesions varies somewhat, however, according to the character of the infecting organism. As the bacterial products are soluble and by means of the blood and lymph circulations reach all parts of the body, so are the changes caused by them, as a rule, equally widespread. On the other hand, some toxins exhibit an affinity for certain types of cells, as the tetanus toxin for those of the central nervous system; or they have a definite relation to certain cells, as that of the toxin of typhoid bacilli to endothelial cells. It is therefore possible to distinguish to some extent between the general effects produced in common by most toxins, and the special, often specific, action of any given toxin.

The theory that bacteria may mechanically produce local disturbances has gradually lost its force, as the result of a more thorough knowledge of the bacterial products and the mechanism of intoxication. The *B. anthracis*, which, because its toxin could not readily be demonstrated, was long supposed to have a mechanical action, has recently been found by Vaughan to possess an intracellular toxin. It is doubtful if any of the pathogenic microörganisms are devoid of the power of producing toxic substances. The thrombi of microörganisms, long considered as a manifestation of mechanical action, are to be regarded as the result of a multiplication occurring after, or perhaps during, the few hours preceding death. Such thrombi are without associated lesions, and are seldom found either after experimental inoculation or in man when the autopsy is made immediately after death; secondary suppuration about such thrombi transfers the condition to the group of pyemias.

Gross Changes.—The bodies of those dying from severe septicemia present little or no rigor mortis; the rigidity comes on early and soon disappears. Decomposition begins early and advances rapidly. In infection with gas-forming organisms local or general emphysematous infiltration may be present. The blood does not clot readily, due probably to an excess of antithrombin, and discoloration of dependent parts is usually well-marked. The lining of the heart, larger vessels, and the serous cavities may be stained by hemoglobin, and occasionally the fluids of the pericardium and other cavities may also be discolored from a similar cause. Small petechial hemorrhages may occasionally be seen beneath the skin, the serous membranes, especially pleura or pericardium, and less frequently within the substance of various organs. In the intestine, hyperemia with either petechial or diffuse hemorrhage may occur. The minute hemorrhages in these locations are more frequently found in pyemia, and are supposed to represent extravasation about minute emboli; they are especially associated with malignant endocarditis. Frequently, however, distinct changes in the vessel wall are found (Howard and more recently Mallory), and it is possible that these may be due to an endotheliolytic substance of bacterial origin. Occasionally the hemorrhages are so numerous as to justify the term hemorrhagic septicemia. Several attempts have been made to demonstrate bacteria in direct relation to those lesions, but the results are contradictory. Occasionally the coagulability of the blood is increased, due apparently to an abnormally high calcium content.

The spleen, in most cases, is more or less swollen, deeply congested, and of lessened consistence, and at times semidiffluent. The capsule in acute cases is tense, and on incision retracts, allowing the softened dark red pulp to protrude. On section the Malpighian bodies are more or less obscured by the increase of pulp and occasionally cannot be recognized. In other cases, although the organ is swollen, its substance is quite firm, and the Malpighian bodies appear as greatly enlarged grayish bodies. If seen after the height of the process, the spleen may be soft and lax, with a wrinkled capsule, the result of volume lost in the subsidence of the congestion and the diminution of the pulp.

The heart, liver, and kidneys present the characteristic appearance due to cloudy swelling and fatty transformation, though this appearance is often obscured by an intense congestion. Œdema of the kidney is not unusual, and small hemorrhages may be present in all these organs. True hemorrhagic nephritis is a rare complication. The lymph nodes are usually swollen, congested, and œdematous. Congestion and œdema of the lung, with or without bronchitis, are quite constant, and not infrequently irregular areas of lax pneumonia are found.

In those cases—the so-called cryptogenetic infections—in which a local lesion was not discovered during life, it may be found at autopsy in the genito-urinary, gastro-intestinal, or respiratory systems, or perhaps in an inflammation of the middle ear, or in an obscure bone lesion; on the other hand, no portal of entry may be discovered.

Histology.—This includes a study of the lesions observed in man and of the experimental intoxications in animals. The conclusions herein

given are based principally upon Flexner's study of toxalbumin intoxications, the studies by Councilman, Mallory, and Pearce of diphtheria, Mallory's investigation of typhoid fever, and the studies by Homén and his associates of streptococcus infection.

The lesions of which we know the most are those of diphtheria, because the changes can be studied, not only in the human individual suffering from the disease, but also in animals by utilizing the very definite toxin of diphtheria. The first complete study of the general lesions in diphtheria was made by Oertel, who demonstrated that the most constant and widespread lesion is a hyperplasia of certain cellular elements, followed later by focal areas of necrosis. This is best seen in the spleen and lymph nodes. The cells which proliferate are, as a rule, endothelial, and have those characteristics best described by the term epithelioid. These cells possess a low grade of phagocytic power.

Councilman, Mallory, and Pearce have shown that the distinctive lesions of diphtheria are the result of proliferation, phagocytosis, and degeneration. The proliferation of the endothelial cells gives rise to an accumulation of cells not unlike the epithelioid cells of tubercle. These engulf and destroy the lymphoid cells, thus explaining in part the nuclear fragmentation which in part, also, is due to necrosis of the large cells themselves. These lesions are due solely to the toxic substance brought to the lymph node. These investigators emphasize also the presence of large numbers of plasma cells in the spleen.

All toxins have more or less power to produce degenerative lesions, as cloudy swelling or fatty metamorphosis in the liver; small hemorrhages and infiltration of lymphoid cells are also not infrequent. In diphtheria and typhoid fever, and less frequently in scarlet fever, minute necroses usually spoken of as focal necrosis may occur. These necroses both Flexner and Reed, as the result of experimental investigations, consider to be due to the direct action of toxic substances. Mallory, on the other hand, explains them by the formation of small emboli of endothelial cells. Flexner presupposes an injury to the wall of the vessel allowing transudation to take place. Councilman, Mallory, and Pearce describe two forms of necrosis in diphtheria, one about the central vein, and the other in the form of disseminated nodules. They are inclined to regard both as due to capillary obstruction plus the action of a toxic substance.

The heart in all forms of intoxication is the seat of cloudy swelling or fatty change. In some diseases, however, as diphtheria, hyaline degeneration with vacuolization of the fibers and changes in the interstitial tissue are not infrequent. The interstitial changes may consist of a focal accumulation of plasma and lymphoid cells, thus constituting a true acute interstitial myocarditis which may occur independently of degenerative changes in the muscles; or, on the other hand, of a true proliferation of the connective-tissue elements secondary to degeneration of the muscle, and therefore analogous to fibrous myocarditis. From the work of Thomas it is evident also that the heart lesions, in diphtheria at least, may be due to a fatty degeneration of the peripheral nerves. The heart in typhoid fever, scarlet fever, and diphtheria has been thoroughly studied by Romberg, who emphasizes the frequency

of interstitial changes, especially in diphtheria. He believes many of the cases of fibrous myocarditis to be the result of such an interstitial condition occurring in the course of acute infectious diseases. Romberg has also described in connection with the nerves of the heart a round-cell infiltration of the connective-tissue sheaths.

The kidneys, like the heart and liver, are commonly the seat of cloudy swelling or fatty transformation. These changes are most evident in the cells of the convoluted tubules which may also occasionally undergo hyaline degeneration. In other cases exudative and hemorrhagic lesions, involving especially the glomeruli, may be found; or an irregular infiltration of the interstitial tissue with lymphoid and plasma cells. This last lesion has been especially described by Councilman in connection with diphtheria, and its occurrence in scarlet fever has been noted by Pearce. In scarlet fever, and less frequently in pneumonia, proliferative changes in the glomeruli may occur. These may involve the cells of the capillary tuft (capillary glomerulitis) or the cells lining the capsule of Bowman (capsular glomerulitis). Hyaline thrombi may be found in a variety of intoxications in the capillaries of the glomeruli.

The most comprehensive study of the lesions due to the streptococcus toxin is that by Homén and his pupils. In the nervous system was found a diffuse granular degeneration followed by slight necrosis and the immigration of leukocytes. Proliferation of the endoneurium and of the nerve sheaths was also evident. The lesion in the liver consisted of degenerative changes with small areas of necrosis and a tendency to the formation of connective tissue. The lungs showed a low grade of desquamation of alveolar epithelium, exudation of serum, and immigration of leukocytes; a continued administration of toxin caused the formation of connective tissue. The early changes in the heart muscle were those of parenchymatous degeneration; in the latter stages, interstitial changes were sometimes seen. The kidneys showed parenchymatous changes, but no nephritis or cell accumulations. In their investigations they observed that the streptococcus stimulated the phagocytic powers of the leukocytes and endothelial cells. This phagocytosis in streptococcus infection has been emphasized by Ruediger.

All toxic substances act upon the individual cell. The character of the change in the cell depends upon the nature of the toxic agent, and upon the resistance of the cell. The lesions produced by toxins have been very well summarized by Mallory as follows: "The effects which injurious agents, especially the toxins, secreted by bacteria, produce on tissues are manifested in four different ways: (1) By degeneration or necrosis of cells, (2) by exudation from the bloodvessels, (3) by proliferation of cells, (4) by phagocytosis." Mallory believes that strong toxins cause degeneration or necrosis of cells and exudation, while dilute and weak toxins produce proliferation and phagocytosis. As types of the first group he cites the toxin of the *Staphylococcus pyogenes aureus* and that of the *Bacillus diphtheriæ;* the best example of the second group is that of the *Bacillus typhosus.* Strong toxins can produce the same processes of proliferation and phagocytosis when sufficiently dilute.

In the same way some organisms, as the typhoid and tubercle bacilli,

which ordinarily produce a mild toxin and cause proliferation, may, especially when the organisms are massed in large numbers, produce a concentrated toxin capable of causing necrosis and purulent exudation. Phagocytosis is most frequent in those infections in which a mild toxin is formed, as in typhoid fever, although it may occur to a limited extent under other conditions.

Pathology of Pyemia. — Any pyogenetic microörganism capable of existence in the blood stream may cause pyemia. In considering the pathology of pyemia it is necessary to discuss the manner in which the microörganisms enter the blood stream and the conditions which determine the secondary localization in the various organs. In the majority of local suppurative infections followed by pyemia the invasion of the blood is not direct, by the passage of the organism through the vessel wall, but indirect as a result of an involvement of the vessels, usually a vein, in the inflammatory process and the consequent formation of thrombi. From these infected thrombi small particles containing bacteria pass into the general circulation and, reaching vessels too small to allow their passage, become impacted. Whereas a bland embolus would cause a simple infarction, these infected emboli, through the microorganisms which they contain, cause local suppuration. A somewhat similar mechanism is seen in malignant endocarditis; small fragments of the exudate or of the thrombotic masses on the valve are swept into the blood-stream and cause, upon impaction, embolic abscesses.

Not only in man, but also in experimental studies upon animals, it is seen that pyemic abscesses develop much more readily when the cocci are adherent to some inert substance capable of mechanically plugging the smaller vessels. Thus Ribbert, in his classical experiments, found that the injection of cultures of the *Staphylococcus aureus* seldom caused abscesses in other organs than the kidney. When, however, he injected cultures scraped from potato with small particles of the potato substance adherent a localization occurred in other organs; indeed, various grades of pyemia could be produced by varying the size of the potato scrapings.

Occasional cases occur, however, in which the emboli do not contain portions of blood-clot but are composed of microörganisms only. Such, possibly, may originate by slow growth in lymphatic vessels, and enter the blood-stream as definite colonies or clumps which are finally arrested in the capillaries. Rarely, as in the case cited by v. Kahlden, a thoracic duct involved in an acute abdominal inflammation may be the point of origin of emboli. Such dissemination is analogous to that occasionally occurring in connection with tuberculosis and cancer involving the thoracic duct. Again, it is possible that single organisms may find foci of altered or injured tissue favorable to their multiplication. This question of *locus minoris resistentiæ* is illustrated in the experimental production of endocarditis and osteomyelitis. The former can readily be produced if the valve is mechanically injured before injecting the microörganisms into the blood-stream; the latter if a bone is first fractured. Further illustration is afforded by the experimental study of Cheesman and Meltzer, who found that by mechanically injuring

various tissues they could cause bacteria circulating in the blood to settle in any place they might select.

It is evident therefore that while embolism is an important factor in the production of pyemia, it is not essential in all cases. Some writers, however, and especially Watson Cheyne, insist that embolism is necessary to the production of true pyemia, and prefer to apply to the condition frequently called "chronic pyemia," due to abscess formation in injured tissues, the term "multiple abscesses." This distinction would appear to be unjustifiable in view of the commonly accepted definition of pyemia—septicemia with multiple secondary abscesses. Indeed, it is evident from our general knowledge of the conditions leading to inflammation that the local injury is the essential condition; and that even with an infective embolus it is probable that inflammation does not begin until the surrounding tissue has been rendered less resistant by an ischemia, the mechanical result of the occlusion of the vessel.

The site of the secondary localization depends largely on the portal of infection. In inflammations accompanied by thrombophlebitis the emboli are usually arrested in the lungs, though an open foramen ovale may allow the passage of large masses to the arterial system; or minute emboli capable of passing through the capillaries of the lung may reach the general system. Localization in the territory of the general circulation may result also from emboli arising in a secondary phlebitis in the neighborhood of pulmonary abscesses or from similar masses set free from a malignant endocarditis. Under these circumstances the kidney, spleen, brain, heart, and voluntary muscles are the more common seats of secondary suppuration; less frequently the liver, serous membranes, joints, bones, skin, or eye are involved.

The changes which occur in the tissues about the infective material are those characteristic of abscesses in general: A central mass of microörganisms surrounded by a zone of necrosis, an outer zone of leukocytic infiltration, and between this and the normal structures, granulation tissue.

Portal Pyemia.—An unusual form of pyemia is that in which, as the result of a local infection in the portal system, multiple abscesses occur in the liver with or without general suppurative pylephlebitis. It may arise as the result of inflammatory lesions of the stomach, intestine, or gall-bladder, or, rarely in the newborn in connection with a phlebitis of the umbilical vein. Appendicitis is perhaps the most frequent cause.

Symptoms.—Toxemia.—We distinguish certain general symptoms common to all forms of toxemia, as fever, rigor, general malaise, prostration, rapid pulse, headache, and restlessness; and frequently certain special symptoms peculiar to the toxin of the infecting organism. These special symptoms usually constitute the characteristic clinical picture in certain diseases, as in tetanus, diphtheria, and typhoid fever.

The toxemia accompanying suppurations, the so-called sapremia, due to the *Staphylococcus aureus*, the streptococcus, or other pyogenic organisms, may come on gradually with slight chills, a low irregular fever reaching 100° to 102° F., loss of appetite, sleeplessness, and a general condition of restlessness. These symptoms usually subside promptly

after local treatment. At other times it comes on abruptly, the symptoms reaching their height within twenty-four hours. This happens most frequently when a hitherto localized lesion suddenly and rapidly involves other tissue, and is to be explained by the freeing of a large amount of toxin which, passing into the lymphatics, quickly reaches the blood-stream. The same rapid onset may be seen in a rapidly developing virulent infection of a previously clean wound. The onset is usually, but not invariably, marked by a rigor and a sudden rise of temperature to 103°, 104° F., or even higher. The rigor may be slight or severe and may or may not recur. The usual concomitants of fever, the hot, dry, and flushed skin, thirst, headache, and coating of the tongue are seen. Vomiting is frequent, and may persist; the pulse is rapid and full; the respiration hurried; the urine scanty and high colored. As the intoxication continues, general weakness, frequently to the extent of prostration, develops; at other times the patient becomes restless, anxious, and irritable. In neglected cases or those in which the source of the intoxication cannot be removed, the prostration becomes extreme, and tremors due to muscular weakness develop. A delirium, noisy or of the low muttering type, may become constant, but occurs usually only at night. The tongue becomes dry and brown, mucus accumulates in the eyes, the lips are covered with sordes, diarrhœa occurs, and the feces and urine are passed unconsciously. The skin may be jaundiced or show petechial hemorrhages. This stage may gradually pass into coma, and, with a falling or subnormal temperature, end in death on the third or fourth day after initial symptoms. Other cases continue in a distinctly "typhoid" condition, and die from exhaustion after a longer period. The urine may contain albumin and occasionally a few hyaline casts; in severe cases an acute exudative nephritis may develop.

Septicemia.—The symptoms of septicemia are due to the same cause—an intoxication—as are those of toxemia, and therefore are similar in character, though usually more severe. The initial rigors may be more marked, and frequently persist. The temperature often remains higher (103° to 105° F.), but with daily remissions or even intermissions. The anorexia may be more profound, as is also the "typhoidal" condition, when it occurs. Jaundice is more frequent and of severe grade. Capillary hemorrhages are not uncommon. In addition the patient will show symptoms of the primary disease or from the local focus giving rise to the septicemia.

Pyemia.—This condition, preceded as it is by toxemia and septicemia, has no distinctive symptoms except those due to the secondary suppurative foci, and these are not always conspicuous. The onset is marked by a severe initial rigor and a rapid rise of temperature to 103° or 105° F. These rigors, followed by fever and sweating, occur at intervals of every day, or every other day, and may frequently have more or less periodicity. The constitutional symptoms are similar in character to those of septicemia, but are exceedingly severe. The signs are dependent on the site of the secondary suppuration. Thus cough and dyspnœa point to an involvement of the lung which physical examination may confirm; if the abscess or bronchopneumonia is near the surface of the

lung the clinical picture of pleuritis may develop. Pleuritis may also be a manifestation of pyemia independently of previous lung involvement. In a similar way the peritoneum, the endocardium, the pericardium, the joints, and the meninges may be involved. Abscesses of the kidney may be recognized by pain and tenderness in the lumbar region and albumin, or occasionally blood and pus in the urine; an enlarged tender spleen is suggestive of the changes following embolism of that organ. Often synchronously with the occurrence of embolism the patient will complain of sudden sharp pain in the region affected. Very important lesions may occur in the eye. The central artery of the retina may be plugged by an embolus, causing sudden loss of vision in the affected eye, and later, through the microörganisms present in the embolus, a panophthalmitis may develop. This last condition may be caused also by an embolus lodging in the ciliary region or iris. Occasionally abscesses of the subcutaneous tissues, or of superficial organs, as the thyroid, salivary glands, or testicle, may be present.

Cardiac murmurs are usually heard, and although often functional, the possibility of an acute endocarditis must be considered. The functional murmurs may arise from low arterial pressure with a rapidly acting heart or from anemia, or they may be due to relative insufficiency of one of the valves, usually the mitral. The skin is often of a yellow tinge, and occasionally in severe cases distinctly jaundiced (hematogenous icterus). An erythematous rash of the scarlatina type, but differing in its distribution, is not infrequent. Very rarely a pustular eruption is seen, and in the later stages of the disease petechial or even diffuse hemorrhages. These hemorrhagic lesions are more frequent in cases with endocarditis.

In the more acute cases death often occurs in the second week. The fatal result may be due directly to any one of the secondary lesions of the heart, lung, brain, or meninges, or the patient may pass into a "typhoid" state and die of exhaustion with or without coma. In rare cases death may occur suddenly from impaction of a large embolus in the pulmonary artery, or from cardiac or cerebral embolism.

The more chronic cases are characterized by the formation of fewer abscesses, a milder course, and longer duration. Acute symptoms, as rigor, fever, and pain, occur with each localization, and then subside, with persistence, however, of a temperature that rises daily above the normal with remissions to or below the normal. The secondary lesions are usually in the joints or subcutaneous tissues, or not infrequently in the endocardium. The disease may last for months, but its course is usually progressively downward, with fatal termination.

Changes in the Blood.—Only those alterations accompanying infection by the common pyogenic microörganisms will be discussed here.

Red Cells.—In milder forms of toxemia due to this group of organisms only slight changes in the blood may be evident, but all observers agree that in severe cases a very marked anemia is present. Ewing states that "in no other disease do the red cells suffer destruction so constantly and to such an extent." The average loss of red cells is from 200,000 to 1,000,000 per week, and the diminution persists as long as the infection

continues. The anemia varies according to the character of the case, marked anemia being associated with uterine sepsis and with endocarditis. Cabot gives as the average count for puerperal septicemia, 3,500,000. Nucleated and distorted red cells may occasionally be seen in the second or third week of severe septicemias. The loss of hemoglobin is one of the chief alterations, and is usually in proportion to the loss of red cells. This solution of hemoglobin may lead to distinct hemoglobinemia, causing staining of the body fluids and tissues, jaundice of the skin, and, as mentioned by Ewing, microscopic appearances in the internal organs similar to those of pernicious malaria. Our knowledge of bacterial hemolysins would appear to explain in part this destruction. In severe cases a very rapid diminution in the specific gravity of the blood may be found.

Most infectious diseases, whether associated with an actual septicemia or not, cause a polymorphonuclear leukocytosis, which is especially marked in smallpox, pneumonia, and suppurative conditions. It is absent, or at most transient, in typhoid fever, measles, malaria, and acute miliary tuberculosis. A lack of leukocytosis in those infections commonly having it is always difficult to interpret, since it may indicate an infection of low virulence, or, on the other hand, a lack of power of reaction on the part of the patient. Arneth has shown that if the polymorphonuclear leukocytes be tabulated according to the number of their separate nuclei or divisions of the nucleus, the normal picture will be as follows: 1 nucleus, 7 per cent.; 2 nuclei, 39 per cent.; 3 nuclei, 36 per cent.; 4 nuclei, 16 per cent.; 5 nuclei, 2 per cent. In acute infections the percentage of forms showing one or two nuclei is increased; that is, the picture is "shifted toward the left." This Arneth interprets as due to the flooding of the circulating blood with young forms recently derived from the bone-marrow. The value of the method is not yet certain.

The Opsonic Index.—By opsonins are understood those substances in the blood fluid which render bacteria more susceptible to phagocytosis. The opsonic content of a fluid, such as serum, with respect to a given organism, is commonly measured by the method of Wright. This consists in counting the number of the specific organisms taken up per leukocyte under the influence of the serum of the patient, compared with the number taken up under the influence of a normal serum, the conditions being kept otherwise as nearly comparable as possible. Hektoen believes the opsonins to be a distinct class of antibodies. The conception that natural recovery from infection depends upon the immunity developed in response to the infection is in accord with the studies of antibody formation in infectious diseases. The pneumococco-opsonin in pneumonia, the streptococco-opsonin in erysipelas and scarlet fever, and the diphtherio-opsonin in diphtheria, show a more or less distinct fall in the early stages; as the symptoms begin to subside the opsonin content rises, the highest point being reached a day or two after the height of the symptoms. Later, in many cases, it abruptly falls. Complications affect the curve in much the same way as the original attack. In rapidly fatal cases the opsonin content may never recover after the primary fall.

Complement deviation, which has proved of such value in the diagnosis of syphilis in the form of the Wassermann reaction, is apparently applicable also to the diagnosis of gonorrhœal septicemia, and possibly of other infections.

Portal Pyemia.—Portal pyemia or suppurative pylephlebitis offers certain special symptoms. The liver usually increases rapidly in size, and this enlargement is accompanied by intense pain in the right hypochondrium and tenderness on palpation. Gastro-intestinal symptoms are prominent, usually with vomiting. Large abscesses pressing on the portal vein may cause ascites, and a similar pressure on the large bile ducts, jaundice; these symptoms, however, are not constant. Peritonitis, resulting from rupture of an abscess on the surface of the liver, or by direct extension, may complicate the picture. Exploratory puncture may occasionally demonstrate an abscess and settle the diagnosis. The course of the disease is severe and rapidly fatal.

Diagnosis.—When the general symptoms described in the preceding paragraphs occur in connection with a local suppurative or gangrenous lesion (dissection, autopsy, or other wound, postpartum endometritis, osteomyelitis, otitis media, or local inflammation after operation), and especially if the primary inflammatory condition is a rapidly progressive one, the attendant must attempt to distinguish between a toxemia and a septicemia, and to consider the possibility of pyemia. The differentiation between the first two is difficult and almost impossible without the aid of blood cultures; while a diagnosis of pyemia can be made only when the secondary localizations offer definite symptoms. If, after removal of the local infection, the general symptoms subside, it becomes evident that the trouble was an intoxication; if, however, they persist, a general septicemia in all probability exists. This can be determined absolutely only by obtaining positive results in blood cultures; negative results leave the diagnosis still doubtful. Fortunately such differentiation is not absolutely necessary in deciding upon treatment; it must be remembered, however, that one can obtain no satisfactory knowledge of the value of the various forms of serum therapy, or indeed carry out any satisfactory serum or vaccine therapy until a distinction is made not merely between toxemia and bacteriemia, but more important still between various types of bacteriemia.

The surgeon can usually explain the occurrence of "septic" symptoms by an examination of his incision, the injured tissue, or whatever the local lesion may be. The physician, on the other hand, may be confronted with general symptoms, atypical or unusually severe, developing suddenly in the course of some definite clinical picture, and which he cannot explain. Or he may recognize a condition as septicemia from the onset, with no local disease of any kind and without evident portal of infection. Such obscure conditions may be due to general infections with the pneumococcus, typhoid, or paratyphoid bacillus, *B. pyocyaneus*, the gonococcus, or one of the common pyogenic cocci. In such cases the only means of exact diagnosis, in the early stages, is by a bacteriological examination of the blood.

On the other hand, the importance of finding the portal of entry can

never be too strongly emphasized, for many long-continued septicemias cease only upon the removal of infected teeth or enlarged tonsils, or the treatment of infected sinuses, an otitis media, a posterior urethritis, or other foci of infection. Obscure primary lesions, as osteomyelitis and abscess of the genito-urinary or alimentary tract, are frequently not recognized. The differentiation of pyemia from septicemia depends on the secondary manifestations. Septicemia or pyemia secondary to an obscure suppurative focus is easily confounded with typhoid fever, acute miliary tuberculosis, or malaria.

Malignant endocarditis, in the broadest sense of our definition of pyemia, is a pyemic manifestation. It is a secondary condition, the result of a bacteriemia of definite or unknown origin, and is frequently accompanied by other suppurations. Moreover, through embolism it usually causes other abscesses. Suppurative arthritis following acute infectious diseases, as scarlet fever and gonorrhœa, is really a mild form of pyemia. Pyemia may complicate almost any one of the infectious diseases, for suppuration is not due to any specific organism or group of organisms, but may be caused by a great variety of bacteria.

Prognosis.—This depends in toxemia on the type of infection, the severity of the intoxication, and the resistance of the individual. In surgical and obstetrical infections the general symptoms usually subside promptly after proper treatment of the local lesion from which the toxic substances are absorbed. Streptococcus toxemia is considered more serious than other forms. The resistance of the individual is an important factor, some persons resisting an intoxication to which old and debilitated subjects succumb. Local lesions which cannot be reached surgically, or those accompanied by thrombosis, always warrant a guarded prognosis because of the possibility of the development of septicemia or pyemia. The time which elapses before proper treatment is inaugurated has an important bearing on the result. In some diseases, as pneumonia, typhoid fever, and diphtheria, in which the toxemia may be out of all proportion to the fever and the extent of the local lesion, it is of serious prognostic import.

Jacob gives the following figures concerning mortality in septicemia from four of the common organisms: Staphylococcus, 88 per cent.; streptococcus, 83 per cent.; pneumococcus (including pneumonias with pneumococcemia), 52 per cent.; colon bacillus, 41 per cent. The prognosis is to some extent related to the number of organisms which can be determined only by the plate method. The surgical forms of pyemia and those accompanied by ulcerative endocarditis, meningitis, and suppurative pylephlebitis or extensive visceral abscesses are almost invariably fatal. In the so-called chronic pyemia and the milder acute forms with suppuration in the joints, or other localities, recovery frequently follows.

Treatment.—The treatment of the local foci giving rise to these three conditions belongs chiefly to the surgeon and to the specialists, ear nose, throat, and genito-urinary, and insofar will be but briefly touched upon. That all foci of suppuration, whether primary or secondary, shall be evacuated when possible and thoroughly cleansed or drained

is the first requirement. Under such treatment a toxemia usually subsides rapidly and the chances of controlling septicemia or pyemia are increased. Thus in renal pyelitis local treatment by irrigation of the renal pelvis, possibly with subsequent injection of one of the silver salts, may be of aid. The difficulty of locating every focus of infection is often great, and it is never to be forgotten that the foci may be multiple. One common source of infection perhaps more frequently overlooked than others is the mouth (teeth and gums). Hunter has pointed out the importance of a thorough cleansing of all tartar, sordes, and crusts from the teeth and gums, and of the use, where the gums are septic, of antiseptic solutions, of which he especially recommends carbolic acid (1 to 60). Bridge work, fillings, and old roots, should they become septic, must be promptly removed. In addition to drainage in the treatment of local foci, passive congestion is of value and may be secured by Bier's hyperemia, by cupping, or by heat.

The treatment of the systemic intoxication or infection may be considered under three headings: General treatment, measures directed toward stimulating the specific defensive mechanism of the body, and specific measures designed to neutralize the toxins or to destroy the invading organisms.

In the *general treatment* the most important factor is absolute rest in bed. Fresh air, which has proved of such value in tuberculosis and pneumonia, may be of value also in the pyogenic septicemias. The food should be the most easily digested, given at frequent intervals, and as abundant, that is should maintain as high a caloric value, as the gastro-intestinal tract will care for. The patient must not be starved, must be urged to drink water freely, and water may also be given by enteroclysis. Alcohol in the form of brandy and whisky has been highly recommended. However, it is of interest that according to Friedberger, Wirgin, and others, alcohol given to rabbits in mildly intoxicating doses after injection with an antigen lessens the formation of antibodies. Coal-tar products for the reduction of fever are of little value, but hydrotherapy may be employed. Regarding the value of quinine there is difference of opinion. Strychnine or digitalis is probably of value when stimulation is required. Dixon and Harvey have found, however, that in the cat subjected to either cobra or diphtheria toxin, the responsiveness of the centres to drug action is gradually lost, but that after the effectiveness of drugs is past the circulation is still markedly influenced by the introduction of normal saline solution. As this procedure is an aid in calling forth a hyperleukocytosis, and also in favoring elimination, it must not be forgotten, especially in sudden severe intoxication with collapse. Pain, vomiting, diarrhœa, and the often obstinate anemia can be treated only symptomatically, always avoiding the use of any drugs by mouth that may impair the function of the stomach. Administration of drugs hypodermically or by rectum is often of value.

Stimulation of the *specific defences* of the body deals chiefly with increasing the number of circulating leukocytes or increasing their efficiency by raising the opsonic index. It was found by Loewit and Richter that injection of albumoses called forth a leukocytosis, and by

Hahn that in the presence of such a leukocytosis the organism was somewhat more resistant to the effects of bacterial invasion. Later Hofbauer employed injections of nuclein to increase the number of leukocytes in the circulating blood. However, Pankow showed that the effect of the nuclein injections is largely due to the normal saline used as the solvent, and that by subcutaneous injections of simple physiological salt solution the same result may be obtained. The most active agent for inducing hyperleukocytosis is probably collargol. Dunger has shown that intravenous injection of collargol suspensions caused a prompt destruction of from 40 to 80 per cent. of the circulating leukocytes, a stimulation of the bone-marrow, and within twelve hours a replacement of the destroyed leukocytes by young cells to a number considerably in excess of the original count. This destruction of the leukocytes is, he believes, responsible for the chills that frequently follow intravenous injections of collargol and, at least in part, for the increased output of nitrogen and purins demonstrated by Ascoli and Izar after similar injections. This method has been rather widely used in the treatment of septic conditions. The usual dosage is from 0.05 to 0.2 gram of collargol in 2 to 5 per cent. suspension, given intravenously, daily, for several successive days. Albrecht uses 1 to 2 cc. of a 5 to 10 per cent. suspension and injects very slowly into the vein from a syringe. Care must be observed to avoid injecting any sediment, as in a few cases dyspnœa and collapse have occurred, attributed to this error in technique. Typically the injection is followed in from one-half to four hours by a chill and a sharp rise in temperature, and then within twelve hours by a sharp fall in pulse-rate and temperature with improvement in the subjective symptoms. From the results reported from this treatment in septicemia, the severest cases, or those having a virulent, purulent, local focus, show no improvement, while milder cases of septicemia, or cases of prolonged subacute toxemia, are often strikingly benefited.

To raise the opsonic index, the use of vaccines by the method of Wright, or often without estimations of the index, is commonly employed. The use of stock vaccines is often unsuccessful when autogenous vaccines give excellent results. Cases of puerperal streptococcic septicemia have proved especially amenable to this treatment. As to dosage, Hektoen gives the following table; the smaller figures are the initial dose:

Bacteria.	Number of dead organisms.
Staphylococcus	25,000,000 to 1,000,000,000
Streptococcus	5,000,000 to 500,000,000
Gonococcus	1,000,000 to 200,000,000
Pneumococcus	1,000,000 to 300,000,000
B. coli	2,000,000 to 1,000,000,000
B. Friedländer	4,000,000 to 8,000,000
To which may be added from Ofenheim:	
M. tetragenes	2,000,000 to 150,000,000

Serum Therapy.—At present successful serum treatment is practically limited to diphtheria and to meningococcus septicemia, although antitetanus serum is invaluable as a prophylactic measure, and possibly exceedingly large doses of antistreptococcic serum may be of some

value if employed at the very onset of a streptococcic infection. This inefficiency of serum treatment is due in part to the differences in the chemistry of the bacteria and the manner in which toxins are secreted, and in part to differences in the mechanism of infection. The immune sera in the present state of our knowledge may be divided into (*a*) the antitoxic sera, (*b*) the bactericidal sera, and (*c*) those which are neither antitoxic nor bactericidal, or but slightly so, but which aid apparently by assisting the protective mechanism of the body. To the first group belong the antidiphtheria and antitetanus sera, each of which contains a true antitoxin for the soluble toxin of the diphtheria and tetanus bacillus respectively. The neutralization of the toxin by the antitoxin in each of these sera is apparently chemical in character, and analogous to the neutralization of an acid by a base. Unfortunately for the success of the general treatment of toxemia by antitoxic sera, the diphtheria and tetanus bacilli are the only important pathogenic organisms which produce soluble toxins. The clinical use of tetanus serum is unsatisfactory, owing to a peculiarity which the tetanus toxin has of uniting with the cells of the central nervous system. This union occurs early in the disease, is a very intimate one, and the poison when so bound to the cell is not at all, or but slightly, affected by the antitoxin. For this reason tetanus antitoxin gives the best results when it is used early in the disease before the toxins are fixed or when intradural injection, which allows a less diluted antitoxin to come in intimate contact with the toxin-saturated cells, is practised. The antitoxic sera have little or no bactericidal power.

The bactericidal immune sera are produced by immunization with those bacteria (typhoid, dysentery, cholera, etc.) which are usually described as possessing intracellular toxins in contradistinction to the soluble toxins of the diphtheria and tetanus bacilli. Such sera are not antitoxic or but slightly so. Their bactericidal power can readily be demonstrated experimentally, but when applied clinically so great an amount of serum must be employed that its use is impracticable. Moreover, owing to differences or irregularities in complement activity, the mechanism of bacteriolysis in man is not analogous to that in carefully planned experiments. When these problems are solved rational treatment of bacteriemia may be expected.

The third group, but recently separated, includes the streptococcic, and possibly the staphylococcic, pneumococcic, and meningococcic sera. These have doubtful bactericidal power and are but slightly or not at all antitoxic. They act apparently either by stimulating certain cells (phagocytes) or by so altering the infecting organisms that they may readily be destroyed by these cells. No satisfactory antistaphylococcic serum for clinical use has yet been prepared.

Owing to the high fatality caused by the streptococcus and the frequency with which infection, either primary or secondary, occurs, much attention has been given to the preparation and mode of action of antistreptococcic sera, but its use therapeutically has not been very satisfactory. On the other hand, the value of Flexner's antimeningococcic serum has been shown to be very great.

CHAPTER X

TETANUS

By JAMES M. ANDERS, M.D., LL.D.

Synonyms.—Trismus; Lockjaw; Opisthotonos; Wundstarkrampf.

Definition.—Tetanus is an acute infectious disease caused by the toxic products of the tetanus bacillus. It is characterized clinically by painful muscular spasms, affecting first and principally the masseter muscles and those of the neck (*trismus*), and secondly, those of the trunk, especially the extensors of the spine and limbs (*opisthotonos*). The disease is endemic and rarely epidemic in large centres of population. Occasionally there are small epidemics, the origin of which can be definitely traced, as a rule. These have received various names according to the special circumstances under which they develop, giving rise to so-called vaccination tetanus (from the use of tetanized vaccine), diphtheria tetanus (due to the use of contaminated antitoxin), and tetanus neonatorum, occurring in newborn children, *e. g.*, where cases have developed in the service of the same midwife. Moreover, hospital epidemics have been known to follow the use of infected vaccine virus and catgut sutures.

The so-called idiopathic or "rheumatic" tetanus does not exist, the disease being invariably traumatic in origin. This dictum receives striking confirmation from the results of a review of 1201 cases by Anders and Morgan.[1] The incidence of the affection is gradually decreasing. A distinction into acute and chronic forms has been made. The latter variety is termed idiopathic or medical tetanus; it presents the same symptoms as the traumatic form, though less severe, and runs a longer course.

Etiology.—Bacteriology.—In 1885, Nicolaier discovered the *Bacillus tetani*. It is a long, slender rod, one end of which is often occupied by a spore; this distends the cell into a pin or "drumstick" shape. The bacillus is 2 to 4μ in length and 0.3 to 0.5μ in thickness, but longer and thicker rods may be found in the cultures. It grows at ordinary temperatures, more rapidly still at the temperature of the body, and in milk, gelatin, and agar-agar; it is motile, is easily stained by Abbott's method, and is purely anaërobic. By means of Ehrlich's method, the fully developed spores may be stained. Kitasato was the first to make pure cultures; this is difficult, since the presence of the smallest amount of oxygen interferes with their growth. The bacilli can be isolated from the wound in which they develop, but do not enter the circulating blood,

[1] *Journal of the American Medical Association*, July 29, 1905.

and therefore are not found in the viscera. Neither do they grow upon superficial wounds as a rule, owing to their anaërobic nature.

If pure cultures are injected into animals, typical lockjaw ensues, but it would appear to be essential to lower the resistance of the infected locality in order to obtain the virulent effect of the organism. The bacillus produces a toxin, which, when inoculated, causes the lethal symptoms of the disease without the presence of the specific organism. Brieger has obtained two poisons from sterilized pure cultures, terming the one "tetanin" and the other "tetano-toxin," both being virulent poisons. These alkaloidal substances cause the tonic spasms, so that tetanus is classed as an intoxication.

Mode of Action of the Toxins.—According to Tiberti,[1] whose long series of experiments corroborates the work of Meyer and Ransom, the toxin passes to the nerve centres not by way of the lymphatics of the nerve, but through the plasma of the nerve fibers. It is necessary, however, that the axis cylinders preserve their normal integrity. The so-called local tetanus is brought about by subcutaneous injections of the toxins or inoculation of special nerves.

Bacillus Tetani Outside the Body.—In the outer world the *Bacillus tetani* is found in many localities (manure, garden soil, street-sweepings, putrefying liquids). It is to be recollected that tetanus spores brought to a new locality may preserve their virulence for years; they may be contained in dust and carried into wounds and also into the respiratory and alimentary tracts, where they may set up their specific lesions in the presence of a diseased mucous membrane. Inoculations with the feces may give rise to the disease in man. MacFarland, from an analytical study of 95 cases of tetanus complicating vaccination wounds, concludes that the tetanus organism may be present in the vaccine virus, being derived from manure and hay.

Predisposing Causes.—(1) *Traumatism.*—While it is undisputable that tetanus may be caused by any sort of wound or breach of the surface, in the investigations by Anders and Morgan, it was found that the preponderating proportion of cases occurred from severe contusions with penetration of foreign bodies. These researches also corroborate the accepted view that the common sites of infection are the extremities, notably the hands and feet. Thus, in 863 cases in which the infection atria were noted, the arms and hands were the gateway for the poison in 294 and the legs and feet in 347 cases, the hands alone in 226 and the feet alone in 280. It was found to be frequent after gunshot wounds of the extremities and "Fourth of July hand injuries." Next to the extremities comes cephalic tetanus, with 53 cases. Finally, the figures indicate susceptibility of all parts of the body to the poison.

2. *Geographical Location.*—The disease is most common in tropical regions, although widely diffused throughout all civilized countries. The sections of the United States in which tetanus is most frequent are "northern New York, along the Hudson Valley, Brooklyn, and the surrounding districts of Long Island, southern Pennsylvania, Virginia,

[1] *Centralblatt für Bakt. u. Parasit., Orig.*, 1905, Band xxxviii, p. 625.

Georgia (at least about Savannah), southern Louisiana, Indiana, Illinois, and southern California."

3. *Seasons.*—The incidence is decidedly influenced by the different seasons. In the collective investigations cited above, the seasonal occurrence in 687 cases showed the following numerical order: July, 129 cases; October, 75; September, 68; June, 61; August, 59; May, 57; November, 47; April, 42; March, 41; December, 37; February, 36; January, 35. The Fourth of July celebrations explain the great increase in July cases.

4. *Age.*—Tetanus is most common between ten and thirty years of age, if we except tetanus neonatorum. The peculiar susceptibility of the newborn is due to wounds of the umbilical cord which serve as infection atria. The age in 583 of our cases showed between ten and fifteen years, 130, and between five and ten years, 99. From the fifth to the fifteenth years, 299 cases occurred (39.3 per cent.), from fifteen to twenty-five years, 145 cases (24.9 per cent.), from twenty-five to thirty-five years 86 cases (14.8 per cent.), and above fifty years, only 14 cases.

5. *Sex.*—In 981 cases of the above series, there were 778 males and 203 females. The greater incidence in the male is readily explained by the more frequent occurrence of wounds.

6. So-called idiopathic tetanus is believed to follow exposure to cold or sleeping on the damp earth, but according to the most modern view there is in all cases a wound or injury of the skin or mucous surfaces, however trivial, which serves as a portal of entry. The only tenable position is to regard colds and catarrhal affections as favoring causes.

7. The robust are more receptive than the weak.

Special Pathology.—A careful postmortem examination often reveals small wounds, abrasions, or evidences of injuries or penetrating foreign bodies, most commonly in the hands and feet. Splinters are sometimes discovered under the nails. The wound or injured part may show the presence of pus, collateral hyperemia, and more or less hemorrhagic extravasation. The nerves leading from the wound are often the seat of inflammation. There are no constant changes in the brain or cord.

In acute cases the density of the cerebral tissue is increased and the gray substance is distinctly hyperemic. In the chronic form the brain and meninges are somewhat œdematous, and minute hemorrhages have been observed. Congestion of the nerve centres of the medulla and cord often resulting in inflammation and softening is commonly noted. Perivascular exudations and granular changes in the nerve cells are observed.

Immunity.—Behring and Kitasato have produced artificial immunity in animals by the inoculation of cultures of the tetanus bacillus after the addition of iodine trichloride to diminish their strength.

Symptoms.—The duration of the period of incubation in human tetanus in the acute form ranges from a few days to two weeks, the usual period being from seven to nine days, while in the chronic, all the way from two weeks to months after the injury. There are exceptional instances in which the incubation period is less than twenty-four hours.

Symptoms of Acute Tetanus.—In a minority of the cases, mild prodromes, such as headache, pain in the back, languor, and slight rigidity of the extremities, are present for a short period. In many cases the patient quickly finds that he cannot open the mouth without great difficulty, and there is soon bilateral tonic spasm of the masseter muscles (*trismus*). More commonly, perhaps, the patient first complains of stiffness and tension in the muscles of the neck; this is followed, after a day at most, by spasm of the masseters, which renders the facial muscles immobile and locks the jaws (*lockjaw*). The rigidity of the muscles of the back of the neck is shown by the retraction of and partially successful attempts at raising the head. Rose points out that participation of the cervical muscles is evidenced by the fact that the patient can hardly touch the chest with his chin. The physiognomy is characteristic; it is immobile, the forehead commonly wrinkled, the eyes partly closed and drawn in, the corners of the mouth retracted, and the lips protruded, producing a distinctive smile—*risus sardonicus*.

At this time the teeth are, as a rule, firmly clenched, and a little later the muscles of the body become rigid; first the trunk (*orthotonos*) and then all the muscles of the entire back become affected, bowing the spine, the convexity presenting anteriorly (*opisthotonos*). After a couple of days the rigidity of the anterior abdominal muscles (especially of the recti) is observed, and their contractions may throw the body forward —*emprosthotonos*. Finally, nearly all of the voluntary muscles manifest tonic, preceded by clonic, contractions, although those of the arms usually escape. Curiously enough, in contrast with the upper extremities, the legs show marked rigidity in extension. The patient assumes the lateral decubitus by preference, as a rule, and maintains almost absolute quiet; he is readily disturbed.

Voluntary urination often becomes impossible, and the same is occasionally true of defecation. From time to time exacerbating, convulsive seizures accompanied with most agonizing suffering, thoracic oppression, dyspnœa, and more or less cyanosis occur. The diaphragm may be similarly involved, causing sharp, lancinating pains at the base of the chest. In one patient "convulsive dysphagia" (as in hydrophobia) was noted. These spasms are reflex in origin. Convulsive seizures can usually be induced by slight external irritation, *e. g.*, by touching. All of the reflexes are exaggerated, but the sensorium remains unclouded. Kernig's sign is early and constant in tetanus (Rostowzew).

Profuse sweating is commonly observed. Brown has reported a moderate leukocytosis (14,000 per cmm.). Leukocytosis as a symptom of tetanus has not received elaborate mention by writers; it is probably due to the suppuration in the vicinity of the wounds that serve as infection atria. The urine rarely shows traces of albumin, and it has been demonstrated that the urea is not increased. According to Senator, neither creatin nor creatinin show an increase in the urine. It is generally believed that tissue metabolism is practically unchanged. Fever of a moderate degree is generally present, although an afebrile course may be observed. Sudden and extreme exacerbations of fever to 100° or 112° F. occur and are pre-agonal as a rule. Hyperpyrexia, however, is

not invariably fatal; it was present in 2 among the 1201 cases analyzed by Anders and Morgan, both of which ended in recovery. A postmortem rise of temperature may also be observed. The pulse is accelerated, but in the majority of instances only to a moderate extent. On the other hand the pulse rate may be much quickened, and at times a rapid increase to 148 to 180 is noted. Such a phenomenal rise is attended with arrhythmia and a marked falling away in force and volume of the pulse; it is ominous.

A favorable course is indicated by a gradual diminution in the intensity and the greater infrequency of the spasms, while muscular rigidity also slowly disappears. The writer saw one patient in whom apparently favorable relaxation of the tonic muscular rigidity was quickly followed by a fatal degree of heart failure.

The *visceral complications* are few, but pneumonia and acute nephritis are occasionally observed. Inability to expectorate the bronchial secretion, as pointed out by Strümpel, may lead to the development of bronchitis or even of inhalation bronchopneumonia. The extreme violence of the tonic spasm may result in rupture of the muscles.

In the series of 1201 cases reviewed by Anders and Morgan, certain interesting features and complications were revealed. In 1 the trismus was so great that the teeth were crushed down to their roots. In 3 cases, in which no antitoxin was used, extensive desquamation of the skin, similar to that of scarlet fever, occurred. In 3 cases the first symptom was severe pain in the region of the diaphragm. Fracture of the spinous processes of the vertebræ resulted from severe convulsions in 1 case.

Chronic Tetanus.—The symptoms develop less apruptly than in the acute form and are less pronounced. There are cases in which the condition remains incompletely developed, the patient being able to separate the jaws sufficiently to allow of nourishment being given. In such the symptoms may suddenly become aggravated, to be followed, however, by a remission. In favorable cases the intervals of partial freedom from the painful tonic muscular spasms grow longer and thus finally the stage of convalescence is reached. However, in certain cases the sequence is characterized by a gradual progressive intensification of the trismus and other symptoms, at last ending fatally. The course may be greatly protracted, and however mild a given case may be it may suddenly manifest the severest symptoms. Relapses are not uncommon unless the antitetanic serum is used.

Head Tetanus.—This is a special variety first discovered by E. Rose, and due to injuries, often trivial, confined to the distribution of the cranial nerves, particularly the facial nerve. This variety is uncommon, only 5 per cent. of tetanus cases being due to face and head injuries. The most distinctive features are rigidity of the masseter muscles, and spasm of the pharynx and esophagus, paralysis of the face on the side of the injury being usually associated. There are cases in which the spasmodic contractions of the œsophagus suggest a clinical analogy between the disease in question and hydrophobia. The great majority terminate fatally. Willard's statistics indicate that 25 per cent. of the

chronic cases end in recovery, but in the acute form less than 10 per cent.

Tetanus Neonatorum.—The cases are divisible into two classes, *e. g.*, early and late, the former developing several days, and the latter eight or ten days, after birth. The most pronounced feature is trismus, which prevents both crying and the administration of food. Within a day or two opisthotonos supervenes and death soon follows.

A collection of 1307 cases[1] from the United States showed the greatest prevalence in Louisiana, the District of Columbia, Maryland, Michigan, Illinois, and Pennsylvania. In this connection it is of interest to note that the census reports from Louisiana for 1870 and 1880 show a total of 806 cases, of which 642 were instances of tetanus neonatorum.

Sequelæ.—The most common sequel is more or less muscular rigidity which may outlast tetanus for a period of months. Thus in one patient of the series cited above, recovery ensued in eight weeks, but decided stiffness remained for eighteen months. In another instance, acute nephritis followed the cessation of muscular contractions. Paralysis is a rare sequel; Kitasato has produced paralysis in man by the injection of small quantities of tetanus toxin into the femoral vein. Relapses are common; this is especially true of the trismus.

Diagnosis.—The usual history and characteristic mode of invasion, especially the early appearance of trismus, followed by rigidity of the cervical and dorsal muscles, justify an assured diagnosis. There are, however, certain affections which bear a clinical resemblance to tetanus. Chief among these are cerebrospinal meningitis, hydrophobia, hysteria or hystero-epilepsy, tetany, and strychnine poisoning. In the subjoined table the distinguishing features of tetanus and strychnine poisoning are contrasted.

Tetanus	Strychnine Poisoning
Reception of a wound, followed by a variable period of incubation.	Ingestion of strychnine, followed immediately by the symptoms.
Begins with lockjaw; then tonic spasm of muscles of neck; later spreads downward, the arms and hands escaping.	Begins with gastric disturbance or a tetanic contraction of the extremities Hyperesthesia of the retina occurs and objects look green.
Reflex spasms not present at the outset.	Convulsions present from the onset.
Rigidity is persistent, except in the chronic form.	Intervals of complete relaxation.
The course is prolonged.	Course is brief.
Cultures made from the discharges of the wound show the *Bacillus tetani*.	Chemical examination of the gastric contents show strychnine.

Tetany is distinguished by protracted spasms limited to the extremities (the hands in particular), and the laryngeal muscles, with complete intermissions; also by an increased electrical and mechanical excitability

[1] Anders and Morgan, *Jour. Amer. Med. Assoc.*, December 22, 1906.

of the motor nerves and a characteristic posture. Moreover, it occurs chiefly in young subjects and there is no history of a wound.

In *hysteria* or *hystero-epilepsy* opisthotonos may be present, but trismus is rare, and when fixation of the jaws occurs, the contractions of the masseter muscles are manifested at irregular intervals. Hysteria also presents associated characteristic nervous phenomena, and there is no history of a wound.

Hydrophobia.—This can be distinguished by a history of the bite of an animal, by the violence of the reflex spasms of the respiratory apparatus, and the great intensity of the psychical disturbance. A few cases of tetanus have been reported, caused by the bite of an animal, *e. g.*, the dog. If in such instances laryngospasm and dysphagia arise, the resemblance to hydrophobia is close, but the shorter period of incubation and the trismus and opisthotonos of tetanus would serve to eliminate hydrophobia.

Cerebrospinal meningitis shows rigidity of the cervical muscles, and there may be opisthotonos, but true trismus does not occur. Again, the history and the associated phenomena suggest meningitis.

Certain cases of mild trismus will be found on careful investigation to be due to pharyngitis, tonsillitis, inflammation of the sphenomaxillary fossa, or finally, arthritis of the temporomaxillary articulation. In all of these conditions, neither rigidity of the neck nor opisthotonos is present. In doubtful cases, the main element, after excluding the commoner sources of tetanus infection, is a careful local inspection of the oral cavity, pharynx, and the masseters. In tetanus, moreover, on passing the finger into the mouth of the patient, the acute edge of the rigid masseters is felt.

Prognosis.—In the majority of cases death ensues and the mortality is highest in those instances that arise after severe traumatism. The late-appearing cases, following an injury, give the most favorable prognosis. Anders and Morgan analyzed the incubation period of 858 cases with special reference to the mortality rate. It was found that 194 (22.3 per cent.) showed an incubation of five days with a mortality of 58.8 per cent.; 394 developed in from five to ten days with a mortality of 63 per cent.; 148 gave an incubation of from ten to fifteen days with a death-rate of 42 per cent.; and 98 cases developed in from fifteen to twenty-five days with a mortality of 40 per cent. Regarding the duration in 870 cases, it was observed that the highest death-rate occurred on the seventh day, or in 86 cases; the second day showed 71 deaths; the third, fourth, and fifth days were rather constant, with about 50 deaths. From the tenth day gradually, and the fifteenth rapidly, the mortality progressively decreased. Again, of cases lasting five days or less there were 338, with a mortality of 275, or 81.4 per cent.; in those giving a duration from five to ten days, or 231 cases, 144 deaths occurred, or 63 per cent.; and those lasting from ten to fifteen days, 91 cases with 27 deaths, or 30 per cent. Acute tetanus or that which developed within ten days gave a total of 568 cases and a mortality of 74 per cent. On the other hand, 211 cases lasted over fifteen days, with only 18 deaths, or 8.5 per cent. mortality.

Wilson,[1] in an analysis of 52 cases following vaccinia, found the incubation to be longer on the average and the mortality also somewhat higher than in the ordinary variety. With A. C. Morgan, the writer has collected 635 cases, of which 615 died, 4 recovered, while in the remaining 16 the issue was not stated.

Recovery in the newborn is quite rare, and when it occurs the diagnosis may be doubted. Complications of a serious character are rare.

The principal causes of death are given by Cheyne and Burghard, as follows: (1) Severe laryngeal spasm, terminating in fatal asphyxia; (2) spasm of the diaphragm or other respiratory muscles; (3) arrest of the heart's action, this may be due either to spasm or paralysis; (4) profound exhaustion and inanition, and (5) severe hyperpyrexia.

Treatment.—(1) **Prophylaxis.**—Certain measures of prevention are of first importance. The immediate radical cleaning of wounds, in which there is ground for suspecting that tetanus may develop, *e. g.*, those soiled with earth from gardens, punctured and lacerated wounds, is of the highest import. This embraces thorough disinfection and then cauterization. The cauterizing agents must be brought into contact with every part of the wound, hence, punctured wounds must first be laid open. Under certain circumstances, excision of the wounds or even amputation is to be advised. The smallest foreign bodies (splinters) must be removed promptly. Friedrich recommends, in all wounds suggesting the possibility of tetanus, total excision of the focus and foreign body, supplemented by preventive injections of antitoxin. In the newborn the wound at the navel must receive the utmost care and attention to insure successful prophylaxis.

Many of the correspondents during the course of the collective investigations cited above, testified to the great efficiency of the dried serum used as a dusting powder after thorough excision and incision of the infected wounds. Prophylactic injections of antitetanic serum are undoubtedly effective, and should be employed in all cases which call for wound purification. Not less than 500 antitoxic units should be administered for this purpose. Schreck reports his experience as follows: "In 1903 there were 56 cases of Fourth of July injuries treated, with 16 deaths from tetanus resulting; in 1904, 37 accident cases were given prophylactic injections of serum, with the result that no cases of tetanus developed."

Among other local measures may be mentioned carbolic acid, which, according to Baccelli, should be employed by subcutaneous injection. Other writers recommend that the suspected wound be sponged out with the undiluted acid. Again, the ice treatment of tetanus, which consists in immersing the part affected in ice with salt, or putting the patient in a very cold room, *e. g.*, a cold-storage chamber, has been advised; this has been much employed in connection with the local use of the dried serum, with encouraging results, but is in the writer's opinion less effectual than the combined aseptic and antitoxin treatment.

[1] *Proc. of the Philadelphia County Med. Soc.*, vol. xxiii, No. 1, pp. 149–165.

2. **Treatment of the Attack.**—(*a*) The *general management* of the individual case is of considerable significance. The patient should occupy a quiet room from which the light has been in great part excluded. All possible sources of external irritation must be strictly avoided, and a trained nurse should always be in charge.

(*b*) The *diet* should consist of nourishing liquids. The feeding should be systematic, the state of the patient being well considered. In those in whom the amount of food that can be administered by mouth is insufficient, rectal feeding must be resorted to and nourishment may be introduced by means of a small soft stomach-tube or catheter passed through the nares. Care is to be exercised to minimize the disturbance.

(*c*) *Stimulants.*—Although the painful tonic spasms of the muscles depend on a hyperexcitability of the motor tracts, cardiac stimulants should not be withheld when heart enfeeblement supervenes. Alcoholic stimulants are to be employed and the commencing dose should be one-half ounce of either whisky or brandy, to be increased if the effect be favorable in direct proportion to the urgency of the indications. Other stimulants as strychnine, camphor, and digitalis hypodermically are also serviceable.

3. *Medicinal Treatment.*—Medicinal treatment has the double object of allaying the excitability and eliminating the toxins. The first indication is met by the employment of such drugs as opium, chloral hydrate, the bromides, calabar bean, chloroform by inhalation, cocaine, curare, and the like. In my experience the spasms are best controlled by chloroform inhalations, keeping the patient somewhat under the influence of either morphine or chloral during the intervals. In view of the persistency of the spasm, care in the administration of chloroform is necessary.

Opium or morphine is to be given with due caution in view of the fact that it exercises an inhibitory effect upon the respiratory centres, death in tetanus being usually by paralysis of respiration. Despite this theoretical objection many authors regard this as the most serviceable remedy. Unfortunately, massive doses are required in many cases either to induce sleep or afford relief from painful muscular rigidity and convulsions. The best mode of administration is by hypodermic injection. As a hypnotic more may be claimed for the combined use of chloral hydrate and morphine than for the latter alone. The chloral may be given by enema, when there is inability to swallow, in doses of 4 grams (gr. 60) every eighth hour, while the morphine may be used at the same time subcutaneously, the doses being large (gr. ss, gm. 0.03). The heroic administration of chloral is not unattended with danger and cardiac stimulants should be given during its employment.

According to the investigations of Morgan and the writer, the chloral bromide treatment has been more generally employed, and the results obtained have been encouraging. Calabar bean may be combined advantageously with opium or chloral, or employed separately. Cocaine has been injected under the spinal membranes, but has given only temporary relief from the convulsions. Hutchins states that chloretone controls the nervous manifestations. Babes speaks in favor of Baccelli's method, which consists of the subcutaneous injection of 5 to 10 cc.

(℥j to ij) of a 0.5 per cent. solution of carbolic acid along the spinal column, beginning at the neck, every two hours. Kintzing reports excellent results from a solution of pure phenol (10 per cent.) in sterile water. Of this solution, the adult dose was 10 drops diluted, by hypodermic injection deep into the muscles, and repeated every three hours in the beginning, increasing the intervals as improvement manifested itself. Rarely, nitrite of amyl, physostigma, belladonna, cannabis indica, and curare have been found useful. Magnesium sulphate (2 cc. of a 25 per cent. solution) may be injected into the spinal canal after the removal of an equal quantity of cerebrospinal fluid.

4. **Antitetanic Serum.**—The general view concerning the value of antitetanic serum is that, unless given before the appearance of the trismus, or before fixation of the toxins in the nerve cells takes place, it is of little, if any, utility. However, it is possible that large doses are more effectual and success has followed the use of doses of 1500 to 3000 units every four hours. When the antitetanic serum exerts a favorable influence, the spasms recur at longer intervals, and with diminished intensity. Reports of cases in which Tizzoni's dried antitoxin was employed internally were at first decidedly encouraging. The dose of the serum is 2.25 grams at the first dose and 0.6 gram at subsequent doses. Roux and Borrel have found that intercerebral injections of antitoxin offer no decided advantages.

CHAPTER XI

ERYSIPELAS (ST. ANTHONY'S FIRE, THE ROSE)

By JAMES M. ANDERS, M.D., LL.D.

Definition.—Erysipelas is an inflammatory disease of the skin due to a streptococcus infection, and characterized clinically by a tendency to spread through the lymphatics, by intermittent fever, and by moderate prostration. Erysipelas occurs both in an endemic and epidemic form.

Etiology.—The exciting cause is the *Streptococcus erysipelatis* (Fehleisen), but it has been proved that this organism is identical with the *Streptococcus pyogenes*. Petruschky has shown that streptococci derived from non-erysipelatous morbid processes were powerful to produce a typical erysipelas. V. Eiselsberg, E. Fränkel, Widal, and others had previously furnished absolute proof by experiments upon animals that the separate identity of the *Streptococcus erysipelatis* cannot be reliably established. The streptococci of erysipelas flourish in all sorts of culture-media, are very minute although variable in size, and usually assume the form of a serpent or chain-forming coccus of Cohn. They are found principally in the minute lymphatics of the skin, and rarely, also, in the capillary bloodvessels, and are especially abundant as well as active near the advancing edge of the erysipelatous area. They are rarely found in the general circulation, and in blood-serum disappear by the action of the phagocytes. Intra-uterine infection has occurred in exceptional instances. The general symptoms of the disease are due principally to the presence of toxins circulating in the blood.

There is abundant proof that the streptococci multiply outside of the body; they offer great resistance to external influences. This is confirmed by the repeated epidemic outbreaks in hospitals and institutions, resulting from local favoring conditions. The occurrence of an institutional epidemic, however, involves the coincident presence of individual predisposition. Kiliani, Kruse, and other writers direct attention to commencing erysipelas of the mucous membrane of the nose. These cases are not spontaneous, and the habit of "boring the finger into the nose" will explain many cases of facial erysipelas. The process does not always begin at the site of the integumental lesion, the streptococci traversing the lymphatics for some distance before implantation occurs. The streptococci cause diseases other than erysipelas and these exhibit the typical fever-curve of streptococcus infection. Inoculation with streptococci derived from a patient caused typical erysipelas in man. It is claimed that the disease can also be produced experimentally by the staphylococcus.

The *mode of infection* is clear; it may occur from the inoculation of wounds (traumatic erysipelas) or from accidental inoculation in the vicinity of the nose and mouth (facial erysipelas). The next most

favored point of selection is the leg; thus out of 586 cases of the idiopathic variety 517, or 88.2 per cent., were facial; 50, or 8.5 per cent., occurred on the legs and feet.[1] Other parts of the body surface, as the hands or scrotum, are rarely the site of infection. Acute coryza may precede the attack (*e. g.*, in 13 out of 301 cases), and in such cases slight, even microscopic, lesions serve as an infection atrium.

Mode of Conveyance.—Erysipelas is inoculable and less commonly contagious, although as a rule the virus is not highly virulent and therefore is conveyed but a short distance. The organism has been collected from the air of wards occupied by erysipelas patients. The poison is also transferred by fomites, instruments, and unclean hands.

Predisposing Causes.—1. *Season.*—Erysipelas occurs most frequently during the cold, damp months of spring and autumn. The writer has shown by analysis of 2010 cases that 50 per cent. occur during the months of February, March, April, and May, and 15.9 per cent. during April alone. These figures also indicate a rise in incidence, month by month, with slightly varying ratio from August to April, after which there is a rapid decline until the minimum number is reached, in August. It was noted that a low barometer and mean relative humidity invariably correspond with the annual period of maximum prevalence.

2. *Age and Sex.*—From an analysis of 1894 cases the writer found that 25.8 per cent. occurred between the ages of twenty and thirty years. The disease is rare before the tenth year of life, if we except newly-born infants, whose great liability is well established. Of the writer's series (1894 cases) 15 per cent. occurred before the age of twenty, while after fifty years of age the incidence rapidly decreased.

The sex was noted in 1767 cases, and the result showed a greater prevalence among males than females. On the other hand, Frickhinger found in nearly 700 cases from v. Ziemssen's clinic that 26.91 per cent. were males, while 73.09 per cent. were females. The balance of evidence indicates the more frequent occurrence among women.

3. *Previous Attacks.*—Individual predisposition is shown by the frequency of recurrences, although the importance of this factor has probably been overestimated. In 450 instances studied by the writer, prior attacks were noted in 39, or 8.6 per cent. It was observed that recurrences affected principally patients afflicted with protracted suppuration, and especially those suffering from catarrhal lesions of the nares with slight fissures about the nose and mouth. In menstrual erysipelas the recurrences may take place at intervals of four or five weeks.

4. *Family predisposition* exercises an influence in rare instances.

5. *Antecedent Affections.*—The marked predisposing influence of certain chronic diseases, such as phthisis, nephritis, organic heart disease, and alcoholism, has been definitely shown.

6. *Slight Abrasions, Fissures, and Traumatism.*—Minute, even invisible, lesions of the skin and mucous membrane of the nose, or the cutaneous surface of the face or ear, invite infection by furnishing a portal of entry. Women after delivery, and subjects of surgical operations, are

[1] Anders, *Journal of the American Medical Association*, July 22, 1893.

peculiarly susceptible for an identical reason. In the same manner a deeply seated focus, *e. g.*, chronic suppuration and necrosis of the bones, may be an underlying cause for repeated attacks.

7. *Antihygienic Surroundings.*—Hospitals and institutions in which the sanitary conditions are faulty favor frequent outbreaks.

Special Pathology.—Erysipelas is a simple inflammation involving the skin, subcutaneous tissues, and less commonly the mucous surfaces. When the process reaches the subcutaneous connective tissue, suppuration as a rule follows; this belongs to the more virulent forms of the affection. Osler in one case traced an extension of the inflammation from the face along the fifth nerve to the meninges, "where an acute meningitis and thrombosis of the lateral sinus were excited." It is believed that extension inward from the skull by still other routes may also occur. The various viscera may present complications usually of a septic character, and visceral infarctions are not very uncommon. Osler states that of 23 cases of malignant endocarditis 3 were secondary to erysipelas. Simple endocarditis, affecting the aortic and mitral segments, and pericarditis may be noted. Out of a total of 1810 cases (with 119 deaths) the postmortem lesions of pneumonia were observed in 4 instances, acute nephritis in 3, and widespread abscess formation in 8. The streptococci are found in the lymph spaces near the margin of the advancing inflammation, while beyond the confines of the spreading inflammation they occupy the lymph vessels, where they are attacked and may be finally overpowered by the leukocytes.

Symptoms.—**Incubation.**—This varies in duration and ranges usually from three to seven or ten days. During this period prodromes, lasting from a few hours to as many days, may appear; they are anorexia, headache, restlessness, angina with cough, malaise, and slight pyrexia.

Stage of Invasion.—The symptoms are (*a*) general and (*b*) local. The disease is usually ushered in with repeated fits of chilliness or a distinct rigor, vomiting, and a rapid rise of temperature to 104° to 105° F. The temperature usually reaches its maximum, 105° to 106.8° F., on the evening of the third day. After a few days of continued fever the temperature-curve becomes irregular, with marked nocturnal remissions often merging into a distinctly remittent or even an intermittent type. At the end of one week the temperature may decline by crisis, or, after a more protracted febrile period, by lysis. As the result of complications, and in erysipelas migrans, a prolonged and irregular fever is the rule.

An evening rise after a period of normal temperature points to a rekindling of the inflammation, or a relapse. The writer has been able to confirm the observations of Da Costa, Strümpell, and others, that the cutaneous inflammation in erysipelas (particularly erysipelas migrans) may advance to a slight extent even after the temperature has returned to normal. Following a severe attack the temperature may be subnormal for a few days. Czyhlarz[1] reports 29 afebrile erysipelas cases, all in women.

The pulse is accelerated, of good volume, and more or less compressible.

[1] *Berl. klin. Wochenschr.*, September 11, 1911.

The constitutional depression may be great, more particularly in alcoholics. A polymorphonuclear leukocytosis paralleling the violence of the infection occurs in this disease, but streptococci have not been found in the blood. The *nervous symptoms* vary in intensity. Headache and restlessness, with nocturnal delirium, particularly in the severer forms, are commonly present. In the drunkard, delirium tremens may suddenly supervene. The *urine* shows the usual febrile characters, including slight albuminuria in many cases at least.

The tongue becomes heavily furred, and nausea and vomiting are not uncommon. There is constipation as a rule, but diarrhœa may occur. Enlargement of the lymphatic glands is found occasionally in the neighborhood of the erysipelatous area. The spleen is moderately swollen as a rule.

Local Symptoms.—In facial erysipelas the starting-point is usually the bridge of the nose, the affected part feeling hot, tense, painful, and sensitive to touch. Almost immediately a small circumscribed area becomes red, swollen, and shining, and the inflammation then spreads laterally in the direction of the ear, over one or both cheeks, and also upward, but rarely implicating the tip of the nose. The point of election may occasionally be on the ear, the cheek, or the hairy scalp. The erysipelatous zone may embrace not only the entire face and ears, but eventually the scalp and even the neck as well. Separating the affected from the unaffected skin there is a sharp line of demarcation—an elevated brawny ridge presenting a wholly irregular outline. While the inflammation is meandering, beyond its borders small red streaks and spots that grow in size until they become confluent may be observed. Certain natural integumental folds, as the nasolabial and border of the hairy scalp, serve to arrest further extension. In a fully developed case the swollen face, tumefaction of the eyelids, great enlargement of the ears (better marked on one side, as a rule), and swollen scalp, tend to produce marked distortion of the features.

Several subvarieties of the local inflammatory process are recognized. Thus the inflammation may spread to the trunk, the arms, and even to the legs, when it is known as *erysipelas migrans.* In some cases the epidermal layer becomes elevated over circumscribed areas presenting smaller or larger vesicles or bullæ—*erysipelas vesiculosum.* The larger blebs may be attacked by suppuration, giving rise to so-called *erysipelas pustulosum.* In exceptional instances necrosis or gangrene occurs—*erysipelas gangrenosum.* When the subcutaneous tissue becomes involved the local manifestations are violent, the fever continues high though irregular in type, and prostration is marked; this is spoken of as *phlegmonous erysipelas.* The local process may extend in depth until the intermuscular spaces and even the periosteum and bones are invaded. The condition often leads to other varieties mentioned above—*e. g., erysipelas gangrenosum* and *pustulosum.* In the newborn the disease may attack the umbilical cord (*erysipelas neonatorum*). From the navel the inflammation may spread to the thighs and genitals. There is fever, and the patient falls into fatal collapse from the sixth to the tenth day. Certain complications, as gangrene or suppuration, may arise.

Erysipelas may recur, usually in the same locality, due to some deep-seated focus of suppuration—*relapsing erysipelas*. Desquamation attends the subsidence of the erysipelatous process, and the complexion becomes more delicate than before the attack.

Erysipelas of the Mucous Membrane.—From the skin the erysipelas may extend to the pharynx, thence through the Eustachian tube to the middle ear and downward to the larynx, trachea, and even to the bronchi. This may lead to œdema of the glottis. The disease may also attack the mucous surfaces primarily, and this form is ushered in by constitutional and local symptoms similar in character to those met with in cutaneous erysipelas. When it begins in the nasal mucous membrane or throat the local phenomena are not characteristic until, as commonly occurs, secondary facial erysipelas supervenes. There is violent pain, redness, and decided parenchymatous swelling, with a sharply defined outline of the affected mucous membrane. The submaxillary lymphatic glands show enlargement and are tender. The sudden development of stenosis of the larynx with death from suffocation has been noted.

Complications and Sequelæ.—An analysis of 1674 cases by the writer with particular reference to complications gave the following result: Abscess, 105; arthritis, 20; delirium tremens, 10; lobar pneumonia, active delirium, phlebitis, pleurisy, each 7; acute nephritis, 6; synovitis and diarrhœa, each 5; and tonsillitis, 3 cases. In a series of 140 cases Lenhartz observed abscesses 9 times (6.1 per cent.). In 4 of these 9 cases the abscess was located in the eyelid. Abscesses occur most commonly upon the head, but also in other parts. The swelling of the lymphatic glands may proceed to suppuration. The *Sanitary Reports of the Royal Prussian Army* embrace 5606 cases of erysipelas with but 8 cases of severe gangrenous inflammation. Widespread abscess formation may lead to generalized sepsis with fatal exhaustion, and the condition may be due to a mixed infection. Gubler has described endocarditis in the course of erysipelas, and since then Sir Dyce Duckworth, Hale White, and others have reported similar cases.

Soft blowing, functional murmurs may be noted and should be differentiated from organic murmurs. The writer has observed arrhythmia due to myocardial weakness from the action of the toxin on the muscular structure of the heart. In addition to lobar pneumonia, aspiration bronchopneumonia may occasionally appear. The pneumonia which complicates erysipelas may be a streptococcus pneumonia. Lenhartz, in a series of 140 cases, observed acute nephritis 7 times, or in 4.7 per cent. Erysipelas is reputed to be curative of a variety of diseases, more particularly eczema, lupus, carcinoma, and sarcoma. After erysipelas the hair often falls out, but is usually replaced.

Relapses are not so common as recurrences, but are nevertheless not infrequent. Out of 476 cases collected by the writer relapses occurred in 54—*i. e.*, 11.3 per cent.; in 1 of these 5 relapses occurred; in 2 others, 4. The relapse may appear after an afebrile intermission of but one or two days, although commonly the interval is three to five days. It may be of short duration and yet accompanied by rather violent symptoms. In some cases (Frickhinger) the relapse may be afebrile.

Diagnosis.—This is not difficult when the eruption is fully developed and typical. The brawny, ridge-like, advancing margin of the inflammatory process forms a well-defined line of demarcation between the healthy and diseased skin, and is one of the distinctive characteristics. The appearance, seat, and behavior, particularly the tendency to spread, form marked peculiarities. Of less diagnostic importance, although of considerable value, are the acuteness and severity of the constitutional disturbance and the enlargement of lymphatic glands in the neighborhood, as well as the variable course due to the part affected and the presence or absence of complications. A bacteriological diagnosis is often possible by examining the pus or secretion from the nasopharynx, which shows the presence of the streptococcus.

The diagnosis of erysipelas of the mucous membranes is exceedingly difficult, and, as a rule, possible only when preceded or followed by cutaneous erysipelas. Primary erysipelas of the mucous membranes is characterized principally by similar general and local symptoms developing acutely and either preceded or accompanied by a rigor.

Differential Diagnosis.—*Acute eczema* has been confused with erysipelas, but lacks the fever, marked swelling, peculiarly raised advancing border, and mode of progression of the latter disease. Moreover, eczema is accompanied by intense itching. The same points of difference, with a longer course, serve to eliminate *chronic erythematous eczema.*

Erythema nodosum is characterized by nodosities which have their favorite seat in the vicinity of the articulations. *Erythema* is unattended with local heat, swelling, pain, and fever. *Urticaria* has been confounded, but appears in the form of pale red circular, scattered wheals in successive crops (often fleeting within a few hours) and with intense pruritus. *Malignant pustule*, affecting the nose, was mistaken for erysipelas in a patient observed by the writer. The swelling of anthrax is exceeding firm, and presents the characteristic central, depressed scar. A positive discrimination, however, demands a bacteriological and microscopic examination.

Prognosis.—Three main considerations form the basis of prognosis in the individual case: (*a*) The severity of the type of the disease, (*b*) the presence or absence of complications, and (*c*) the circumstances directly connected with the patient himself. As to the first, more or less severe types are sometimes observed as indicated by the degree of fever, its duration, the cardiac rate, and nervous phenomena—delirium, stupor. Of the complications, those fraught with greatest danger are excessive suppuration, delirium tremens, pneumonia (lobar or lobular), acute nephritis, gangrene, phlebitis, pleurisy, pyemia, and œdema of the larynx. The average duration in typical cases under forty years of age is fourteen days, but complications materially lengthen the course.

Among circumstances connected with the patient is *age*. The outlook grows graver (after the fifth year) in proportion to the age, especially after forty-five years. Thus the analysis of 1810 cases indicated that age has a decisive influence upon the mortality after the forty-fifth year. These figures gave a general mortality rate of 6.57 per cent. for hospital cases and 4.16 per cent. for those from private practice; in persons under

forty years the death-rate was only 3.5 per cent., in those over seventy years 46 per cent., and in traumatic cases 14.5 per cent.

The preëxistence of certain chronic affections, notably pulmonary tuberculosis, chronic nephritis, and organic cardiac diseases, not only increase susceptibility, but also augment the mortality as much as 25 per cent. When death occurs it is usually from exhaustion or asthenia.

Treatment.—This may be considered under four heads: (1) Prophylaxis, (2) diet, (3) constitutional treatment, and (4) local measures.

1. **Prophylaxis.**—This has reference not only to measures limiting the spread of the disease, but also to the prevention of a relapse. It is probable that relapses are sometimes due to auto-infection, or a reinfection from without; and to obviate this danger frequent changes of the body-linen and removal to another room during convalescence are advisable. In persons who have suffered from previous attacks a recurrence may be prevented by treatment of some of the predisposing conditions.

The antiseptic treatment of wounds led to a marked decrease in the cases of erysipelas; but strict isolation of the disease from the injured, and, more particularly, operation cases, is the most efficient preventive. It is advisable to isolate all patients with erysipelas, since there may be transmission by contact from the sick to persons apparently free from wounds, fissures, suppuration, or other lesions. Transmission may occur before the erysipelatous character of the disease is recognized. Admission of erysipelatous patients to hospitals should be refused, except to institutions provided with an isolation building, special physicians, nurses, and other employees.

The serious significance of erysipelas in the newborn makes prevention of great importance. Puerperal women should be guarded from all danger of exposure. Bathing with a boric-acid wash (3 per cent.) thrice daily, so as to disinfect the desquamating epidermis, is strongly advised.

2. **Diet.**—A tendency to exhaustion is manifested in the more protracted cases, hence alimentation must be generous. If the temperature be high, the diet should be restricted to liquids given in definite amounts at stated intervals. It should consist especially of milk predigested or diluted with simple water, barley water, or lime water. Albuminized milk, albumin water, animal broths, beef-tea, and bouillon, may be also used. In persons over fifty years of age and in those exhausted by previous disease, an appropriate dietary is of the first importance and may be the means of abridging an otherwise protracted attack. Rectal alimentation should be used if the stomach is upset. Under special circumstances both methods of feeding may be required temporarily to maintain strength. When convalescence begins, and in the lighter cases throughout the attack, pulled bread, toast, well-boiled rice, and eggs, may be allowed. As convalescence advances other solid foods of the more digestible kinds are to be given. It should be understood that appropriate feeding is of greater service than any medicinal treatment.

3. **Constitutional Treatment.**—When the pulse becomes rapid and feeble, the action of the heart weak and irregular, with or without the presence of a dry, brown tongue, stimulants are indicated. Whisky and

brandy are best, the dose being governed by the effect upon the circulatory system. If alcohol fails, other stimulants may be given simultaneously. The judicious use of strychnine has been most serviceable in the hands of the writer, in doses of moderate size, at first $\frac{1}{40}$ grain every fourth hour, to be gradually increased until a favorable effect is produced. Should urgent symptoms arise, strychnine may be administered hypodermically until the blood tension has been restored. Digitalis may also become an invaluable aid during the advanced stages, either alone or combined with strychnine. Under similar circumstances saline injections given subcutaneously or intravenously increase the blood pressure; they may be repeated at intervals of six to eight hours as occasion demands. Diffusible stimulants, as champagne or aromatic spirit of ammonia, are also useful during circulatory depression.

The bowels should be moved gently but regularly by fractional doses of calomel, followed by the daily administration of a mild saline, as sodium phosphate. The sweat glands may be stimulated by sponging the surface with tepid water or water as hot as can be borne; this may be repeated twice or thrice daily. Large quantities of water should be given, to which potassium bicarbonate or acetate may be added.

Attempts have been and are continually being made with various kinds of specific treatment, but these have failed to justify their use. The writer's best results have been obtained with the employment of certain remedies, notably iron and quinine in combination. The tincture of the chloride of iron, first recommended by Hamilton Bell in 1851, has been extensively used by English authorities, and was looked upon by the older clinicians as a truly sovereign remedy. Iron, however, does not deserve to rank as a specific. In 74 cases of erysipelas treated by the tincture of the chloride of iron alone, the average daily quantity being 1 dram in divided doses, at the Pennsylvania Hospital, Philadelphia, by Lewis, Da Costa, Longstreth, Meigs, and others, the death rate was 4 per cent.[1] The dose of the tincture of iron should not be less than 10 to 30 ♏, repeated every second or third hour, according to the severity of the attack. The effect of iron is much enhanced by associating with it quinine, which may be given separately in capsules or milk. In England this remedy enjoys a wider reputation than iron, as the result of the well-known experiments of Binz. The daily dose of quinine should range from 16 to 30 grains; its use may be confined to instances in which the temperature reaches 103° F. or over, and usually in uncomplicated cases the nocturnal remissions become decidedly greater and the course of the disease appears to be somewhat abridged.

Marmorek Knorr, Chantemesse, and others have successfully immunized certain animals (rabbit, donkey, horse) by the subcutaneous injection of highly virulent streptococcus cultures. Instances of its successful use as a curative agent have been reported by Andre, Robinson, and others; it has to be repeated at forty-eight-hour intervals to obtain all its advantages. G. H. Sherman reports uniformly good results from the use of stock vaccines (streptococcic), especially when used early in

[1] Anders: "The Treatment of Erysipelas," *Therapeutic Gazette*, July 16, 1894.

the course of the disease. The dose is 20,000,000 for the adult, and when local improvement with the reduction of temperature does not occur, this should be repeated at the end of twenty-four hours.

Certain symptoms may require treatment. Antipyretics have little or no influence on the fever and are strongly contra-indicated on account of their depressing effect. High fever can be met by the application of ice-bags, cold sponging, or gradually cooled baths. Pain, insomnia, and active delirium are favorably modified by the use of hyoscine hydrobromate (gr. $\frac{1}{200}$ to $\frac{1}{100}$, hypodermically). This is contra-indicated in the presence of feeble heart action. The following may be used: Sodium bromide, gr. v (0.324 gram) every two hours, or gr. xx to xxx (1.2 to 2 grams) at night; potassium bromide, gr. x (0.6 gram), and tincture of cannabis indica, ♏x (0.6 cc.), in combination. Occasionally local discomfort and pain are troublesome features, and are best combated by morphine, gr. $\frac{1}{8}$, hypodermically. The treatment of *complications* must be conducted as they arise.

4. **Local Measures.**—These have always held a prominent place. In three different series, making a total of 247 cases, the remedies most commonly employed, by differentiation, locally, were elm, lead-water, and laudanum, carbolic acid (1 to 40) injected subcutaneously, zinc oxide, mercuric chloride solution, and ichthyol ointment with lanoline. One of the indications is the exclusion of air with a view to inhibiting the growth and development of the organism, which can be best accomplished by the use of carbolized vaseline or carbolized oil. To Huter belongs the credit of introducing the method of injecting carbolic acid (1 to 40). The object is to check the spread of the inflammatory process by inserting the needle at numerous points just beyond the inflamed margin. It is especially serviceable in erysipelas migrans. The local use of a solution of mercuric chloride has been followed by the writer in hospital and private practice with encouraging results.

Tucker recommends the application of a saturated solution of magnesium sulphate in water. This is applied in facial cases on a mask consisting of from fifteen to twenty thicknesses of gauze, of sufficient size to extend beyond the area involved, with a small opening to permit breathing, but none for the eyes. After thorough saturation with the solution, the mask is applied and covered with oiled silk or wax paper; it is wetted often enough to assure a moist dressing—usually every second hour. The dressing should not be removed oftener than once in twelve hours to permit an inspection of the parts.

Ichthyol has been extensively used by Nussbaum, Fessler, Klein, and others, but that it exerts a specific effect lacks clinical support. Agents whose influence is partly mechanical and partly chemical (astringent) have also been employed. Of these collodion and ichthyol-collodion (10 to 50 per cent.) are painted in a tolerably thick layer not only over the erysipelatous area, but also over the surrounding healthy skin for 2 or 3 cm. MacLennan advocates a saturated solution of picric acid as a local remedy.

CHAPTER XII

EPIDEMIC CEREBROSPINAL MENINGITIS

By HENRY KOPLIK, M.D.

Definition.—Cerebrospinal meningitis, or cerebrospinal fever, is an acute infectious disease with a characteristic local lesion in the meninges and tissues of the brain and spinal cord.

Cerebrospinal fever is a term which has been preferred by Osler in an attempt to compare the affection with pneumonic fever or pneumonia. It is certain that he has shown a striking similarity in the course of both affections. The term cerebrospinal fever, however, expresses one part of the symptom complex and does not include the lesions found in the brain and cord. We will, therefore, retain the term cerebrospinal meningitis of the epidemic type, because the striking feature of the disease is that it appears, when prevalent to any extent, in the form of epidemics and is primarily a meningitis of the brain and cord.

America is peculiarly the home of this disease, and it is very difficult in studying the literature and epidemiology to account for this fact.

Character of the Epidemics.—Councilman has attempted to characterize the nature of the epidemics of this disease as distinct from epidemics of other diseases, such as cholera. Certain it is that the disease first appears in isolated places and does not seem to be carried to any extent from one place to another, though it has been shown in Algiers and in France that the disease may be traced along the line of march of troops. No such etiological factor, however, can be pointed to in the epidemics in Boston and New York.

In the author's experience and in that of most writers the disease is most prevalent in the winter and spring. The epidemic of 1904 first appeared in New York with isolated cases in February. The frequency increased and in April and May the largest number of cases occurred. In summer and autumn the disease died out, to reappear late in the winter of 1905. In Boston the first case was observed in June and the disease became epidemic only in February, the greatest number of cases occurring in March, April, and May.

It is a disease of young people, but the prevalence in the Boston and New York epidemics seems to have varied as far as the age was concerned. Children were most affected in the New York epidemic, whereas in Boston the greatest prevalence occurred from the twenty-sixth to the thirtieth year. Leichtenstern shows that in his cases the greatest number occurred before twenty years of age, most frequently between the ages of fifteen and twenty years.

Contagion.—The question of the communicability of the disease has always been a matter of discussion. There can be no doubt that in

certain epidemics, such as that described by Berg in 1893 in New York, there was no instance of the affection of more than one person in a family, whereas in 1904 and 1905 numerous examples have occurred in which two, three, and even four children of a family were affected. The author, in some of these cases, found that another child of the family, having slept in the bed recently vacated by the meningitis patient, contracted the disease. It may be carried from one person to another or from one country to another, according to North, but there has been no authentic example of this in recent times. That is, cerebrospinal meningitis cannot be carried as scarlet fever may, by a second person to a third. It occurs in certain houses, very much in the manner of pneumonia. That the disease is communicable from person to person there is no doubt. It certainly is not communicated through the atmosphere.

One attack does not protect from another; this has been shown by North, Herman, and Kober, who recorded instances of second attacks, some within a year.

There is no doubt that the disease is more prevalent in the crowded quarters of cities than in the sparsely populated parts and where filthy conditions exist than in more cleanly districts. This has been doubted by some, because cases have been found in the better quarter of cities where the hygienic conditions were good, but the writer feels that a careful study of such cases will reveal that they are exceptional and have been communicated or conveyed from filthy and crowded parts of the city where the disease was most prevalent.

The disease occurs in sporadic as well as in epidemic form. Both are due to the same cause. The sporadic cases occur either independently of the epidemic, that is, in different quarters of the city, or in sparse numbers so as not to amount to epidemics. Sporadic cases may occur for some years after an epidemic has run its course. It is not understood why epidemics are not prevalent at such periods. Some have tried to explain these sporadic cases by the morphology of the *Diplococcus intracellularis*, its low vitality and the immunity of the mass of individuals to infection by it, and by the absence of conditions favorable to epidemics and the communicationof the disease by one individual to others.

It may be communicated through the secretions of the mouth, nose and conjunctiva, because the etiological factor of the disease has its habitat on the mucous membrane of these localities and has been demonstrated in the secretion of the conjunctiva and nasal membrane. It has not yet been determined whether the disease is communicated to human beings by insects.

Etiology.—The etiological factor both in the epidemic and sporadic forms is a coccus of the diplococcus type. It was first described by Leichtenstern and more completely described by Weichselbaum in 1887. It is a diplococcus similar to the gonococcus, and has been called by Weichselbaum the *Diplococcus intracellularis meningitidis*.

The *Diplococcus intracellularis* is a micrococcus of the size of the ordinary pathogenic micrococci. The diplococci show an unstained interspace, are decolorized by Gram's stain, may occur in tetrads or in short chains, but do not occur in the form of streptococcus chains, as

described by Jäger. The microörganism is difficult to cultivate and of low vitality. Cultures, in order to be kept alive, must be renewed at short intervals. It grows best on Loeffler's serum and in glycerin-agar, not in the form of profuse streaks but rather in isolated colonies. It grows but feebly in plain agar and is not visible as a growth on potato. In bouillon it gives a slight cloudy sediment at the bottom of the tube. It does not change litmus. In the inflammatory exudate it is especially prevalent in the polynuclear leukocytes, not in the other cells of the tissues, though it may occur outside of polynuclear leukocytes, either in the exudate or in the tissues but not in the cell body. It sometimes is so numerous as to pack the leukocyte and in other leukocytes may not be so numerous. It has been found in certain cases in great numbers in the lungs when pneumonia complicated the meningitis, and here it may occur with pneumococci, staphylococci, and streptococci.

The meningococcus has been found in the secretions of the nose, the eye, the bronchi in pneumonia, in the pus of complicating joint affections. It has been isolated from the blood of patients with the disease by Solomon, Moller, Bettencourt, Franc, and Elser. The last-named writer found it in 25 per cent. of his cases at various periods independently of the severity of the infection. Its occurrence in the nose and the secretions of the nasal mucous membrane of normal individuals is especially interesting in view of the fact that in this locality there occurs normally a diplococcus which closely resembles the meningococcus and which is called the *Diplococcus catarrhalis*. This has been mistaken by many observers for the meningococcus. Its morphology has been described by Ghon and Albrecht, and by the skilled observer can be easily distinguished.

Goodwin and Scholly isolated the meningococcus from the nasal mucus of 50 per cent. of meningitis patients during the first two weeks of the disease and from 10 per cent. of those who came in contact with the patients. These authors, as well as Boldnan, consider the disease transmissible through the nasal mucus from one person to another.

Considering all the data, weight is given to the supposition that the mucous membrane of the nose and the neighboring respiratory spaces is a normal habitat of the meningococcus. This diplococcus is found in the pus of the conjunctivitis which complicates the disease; such a case has been published by the author.

The method by which the infectious agent gains access to the cranial cavity is a matter of speculation. The old theory of Weigert that infection occurs through the mucous membrane of the nose and ethmoid sinuses has been revived in another form by Westenhofer, who contends that the disease is an inhalation infection by the lymphatics through the tonsils, sphenoidal sinuses, the antrum of Highmore and, finally, by direct extension through the sphenoidal sinuses to the hypophysis. He rejects entirely an extension of the infection of the brain through the ethmoid sinuses inasmuch as they are rarely inflamed. A critical inspection of Westenhofer's work is not convincing.

Age and Occurrence.—Prior to the year 1904 the writer had yearly 8 to 10 cases of cerebrospinal meningitis in his hospital service. These

PLATE VII

FIG. 1

Convexity of the Brain. Epidemic cerebrospinal meningitis with death on the fifth day of the disease. Purulent exudate.

FIG. 2

Lateral View of the Brain in the Same Case.

PLATE VIII

Section of the Spinal Cord, showing the Exudate on the Surface, More Marked Posteriorly and Involving the Anterior and Posterior Nerve Roots. Epidemic cerebrospinal meningitis in an adult; death on the fifth day of the disease.

occurred independently of any epidemic. In the years 1904 and 1905, New York was visited by an epidemic of this disease and he was able to collect 119 cases, occurring in his hospital, both in children and in adults. The incidence as to age is as follows: Under one year, 25 cases; one to two years, 13 cases; two to four years, 17 cases; four to ten years, 32 cases; ten to fifteen years, 12 cases; fifteen to twenty years, 7 cases; twenty to twenty-five years, 1 case; twenty-five to thirty-five years, 4 cases; thirty-five to fifty years, 6 cases; and fifty to sixty years, 2 cases. The youngest patient I have treated was ten days old. The greatest frequency, in the author's patients, has been in children below two years of age. Flexner's statistics give the greatest frequency between the ages of ten and twenty years. Between twenty and twenty-five years we had only 1 case. After the age of forty the disease is infrequent. This corresponds to most of the statistics available.

Morbid Anatomy.—The essential lesions are inflammatory in the meninges of the brain and cord, the tissue of the brain, cord, and nerves.

The Brain.—The *meninges of the brain* are inflamed, and there is a purulent, seropurulent or fibrinopurulent exudation, most apparent at the edges of the brain, extending from the optic commissure back over the crura, pons, and medulla. On the surface the exudation is found on the convexity, mostly laterally and for some distance on either side of the fissure of Rolando. Little or no exudate is found along the longitudinal fissure. The meninges of the cerebellum are also involved, principally on the upper surface and upper rim along the choroid plexus.

In acute stages the changes consist mostly of injection and œdema of the meninges. There is little or no exudate. There may be thin lines of yellowish exudate along the sulci, and the pia-arachnoid has a pinkish color due to the intense injection of the bloodvessels. (Plate VII.) In cases dying five to twelve days after the onset the exudate is more abundant and fibrinous and more marked about the base and medulla. In cases which have lasted from fifteen to thirty days there is œdema and thickening of the meninges, with whitish patches apparent on the vertex and at the base of the brain, consisting mostly of organized exudate. At the base of the brain bands of organized tissue may be seen stretching from point to point. The lining membrane of the ventricles may be thickened and the seat of exudate.

The *meninges of the cord* are affected very much in the same manner but to a less degree. In some cases there is little or no exudate; even in cases which have lasted a week and which show marked exudate on the brain there may be little or none visible macroscopically on the cord. Exudate on the cord is most marked on the posterior surface, the amount of subarachnoid fluid being increased and the central canal dilated. (Plate VIII.) In acute cases the ventricles of the brain may not only be dilated but filled with turbid fluid, and the cornua may contain a purulent fluid. The lining membrane, or ependyma, is the seat of changes either of injection or exudate, as is also the choroid plexus. The tissue beneath the walls of the ventricles may be œdematous and softened. In chronic cases the lining membrane is thickened and has lost its luster. It may be covered with granulations. The cavity of

the ventricle is dilated to a varying degree, according to the amount of hydrocephalus which has supervened.

The *tissue of the brain* may be the seat of hyperemia, or hemorrhages in the various parts, and on section there may be thrombi in the vessels, with areas of softening and even abscesses in places. The cranial nerves are found to be embedded in the exudate and on section are swollen and red and the seat of changes to be described. The tissue of the pia-arachnoid is the seat of purulent infiltration, the bloodvessels are filled with blood and leukocytes, and their walls show infiltration with small masses of leukocytes. Throughout the tissue of the pia-arachnoid there are found small areas of leukocytes scattered in the finer granular inflammatory mass. The connective tissue of the pia is infiltrated with cells, principally polynuclear leukocytes. (Plate IX.) There is a peculiar cell found here, and described by Councilman, which measures two to eight times the diameter of the leukocyte, having a large vesicular nucleus and finely granular protoplasm in the cell body. Some of these large cells contain a varying number of leukocytes.

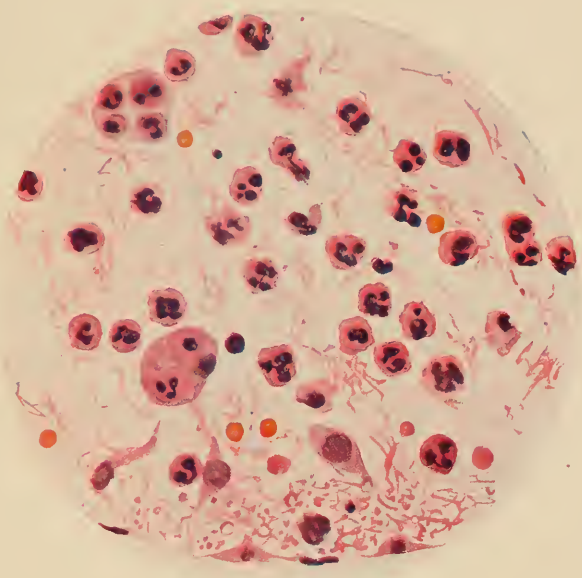
In chronic cases the pia-arachnoid shows distinct changes in the connective tissue resembling cicatricial tissue. There is proliferation of the fixed connective-tissue cells of the arachnoid and those lining the lymph spaces. Nuclear figures are very common in the cells of the connective tissue. Changes in the meninges of the cord resemble in a general way those found in the pia-arachnoid and brain.

The brain tissue shows microscopic changes, which are most marked in cases which have extended over a period of five to ten days or more. The vessels are injected, the tissue itself is œdematous, and the lymph spaces are dilated. Here and there, there is a diapedesis of leukocytes from the meninges into the brain tissue proper some distance from the cortex. There are areas of hemorrhage and extensive softening at times. The ganglion cells show changes of a degenerative nature, although investigations on this point are not yet complete. In chronic cases also the canal of Magendie may be obliterated and there may be marked changes, thickening of the meninges, with connective-tissue proliferation into the tissue of the brain. The neuroglia shows in places an increase of cells, especially with vesicular nuclei and branching processes in the cortex of the brain and in the walls of the ventricle.

The microörganisms are found in the exudate on the surface of the brain and in the tissue of the pia-arachnoid, for the most part in the leukocytes. Very few are found outside these cells. The *Diplococcus intracellularis* may also invade the tissue proper of the brain and cord.

The Nerves and Ganglia.—The changes in the nerves have been particularly studied in the optic, the olfactory, the fifth, seventh, and eighth nerves. Changes in the ganglia have been studied in the Gasserian ganglia, and described by Councilman. The changes in the nerves consist of infiltration of the pia-arachnoid and dilatation of the bloodvessels of the nerve with a purulent infiltration as a direct extension from the inflammation of the brain. In the optic nerve this may reach the optic globe, causing neuroretinitis, and may even proceed to a general inflammation of the tissues of the orbit with bacterial invasion.

PLATE IX



The Exudate of the Early Stage and Inflammatory Reaction in the Pia Mater.

This shows: Swelling cells of the pia; fibrin in the exudate; the leukocytic invas on; new connective-tissue cells; nuclear division; large cells containing three or more leukocytes described by Councilman, Mallory, and Wright.

The ganglia, such as the Gasserian ganglion, may be the seat of purulent infiltration and degeneration to such an extent as to result in the destruction of the nerve cells. The posterior nerve roots of the spinal cord may be the seat of inflammation, the bloodvessels are injected, small collections of plasma and lymphoid cells are found between the individual nerve fibers, which are themselves the seat of degeneration, and the axis-cylinder may show marked changes. The peri- and endoneurium are the seat of infiltration and inflammation. In some cases the pituitary body is the seat of infiltration, necrosis, and atrophy.

Other Organs.—The changes found in other organs of the body are either complicating or accidental. A complicating pneumonia may be of the lobular or croupous type. There may be bronchiectasis and small hemorrhages throughout the lung. In some cases as described by Councilman, the pneumonia was directly caused by the *Diplococcus intracellularis meningitidis*, and the microörganism was found in great numbers in the inflammatory area.

The spleen in some epidemics has been found to be enlarged in the majority of cases. It may, however, be smaller or even normal in size. After the fifth day, as a rule, it may be slightly enlarged and the seat of hyperemia. The lymphatics show no changes outside of congestion and injection. The liver may show cloudy swelling. The kidney may be the seat of acute degeneration and parenchymatous changes.

There are areas of hyperemia and hemorrhage in the skin, most marked in the subcutaneous fat. These correspond to the petechiæ in the skin seen during life. Although there may be abscesses in the skin and purulent infiltration, as yet the intracellular diplococcus has not been found in the skin lesions. In the herpes, both on the face and the trunk, no diplococci have been isolated from the fluid.

Symptoms.—Cerebrospinal meningitis of the sporadic or epidemic type manifests itself in distinct clinical forms. During an epidemic these are more sharply defined than at other times. The first is the so-called foudroyant or malignant form in which the fatal issue may supervene within twelve, twenty-four, or thirty-six hours. In an epidemic these malignant forms are not uncommon. They are most apt to appear, however, either at the outset of an epidemic or at times when it is apparently on the wane. An adult or a child in apparent health complains of slight headache, there is nausea followed by vomiting, fever, and unconsciousness in rapid succession. Death occurs in a short time, consciousness not being regained.

Another form is that in which the patient, in apparent health, is suddenly taken with dizziness or vertigo, vomiting occurs, followed by severe headache, generally of the occipital type; fever ensues, the patient becomes drowsy or even delirious. At this time there may be slight rigidity of the muscles of the neck and a slight Kernig reaction and Brudzinski's reflex. In these cases, after a period varying from hours to a few days, the patient passes into a condition of stupor and delirium, with retraction of the head, opisthotonos, and the full picture of the disease. In other cases this history is interrupted by periods of collapse. A patient taken with fever, vomiting, and headache, is ill for twelve

hours with these symptoms and is perfectly conscious, when suddenly, after an attack of vomiting, he passes into a condition of collapse, with a rapid thready pulse, sighing respiration, and total abolition of reflexes. After rallying from this condition he shows the classical symptoms. In this condition of shock there is nothing characteristic of meningitis; that is, there is no rigidity of the neck, opisthotonos, or Kernig's sign. The patient seems to be in a condition of shock superinduced by the sudden onset and the toxemia resulting therefrom, and from what has appeared to the author rapid distension of the ventricles of the brain.

During an epidemic there is a more puzzling form very frequently encountered. A patient in apparent health will complain of headache, fever, and, in the case of infants, is restless, refuses the breast, vomits once or twice, and then has a temperature curve ranging from 105° F. to normal or subnormal. In the intervals of apyrexia the patient seems quite well and, in the case of infants or children, will play and seem in apparent health. When the temperature rises, however, they complain of slight headache, become drowsy and irritable, and refuse nourishment. In these cases the typical signs of meningitis are not always apparent. The delirium is not constant and may not extend over twenty-four hours. The rigidity at the back of the neck may not be very marked, especially in the case of young infants. If above two years of age Kernig's sign and Brudzinski's reflex may be present, not only when the temperature is high but when subnormal. The most characteristic features are the sudden onset and the prolonged period of fever of the intermittent type. These cases are often mistaken for malaria and are not uncommon in an epidemic of cerebrospinal meningitis.

In many of these cases the onset has been insidious; in others it may have been marked by an attack of vomiting or convulsions. In other cases the disease is masked by some complication such as neuritis. The writer has seen certain cases in which the onset has been marked by slight headache, vomiting, and fever, which continued for a few days, and then the patient developed an intermittent temperature in the absence of headache, with but slight rigidity of the neck, a marked Kernig's sign and severe double sciatic neuritis, which continued over weeks with intervals of intense pain and the characteristic temperature.

In every epidemic there are abortive cases which last but a few days when the fever subsides and the patient makes an uncomplicated, at times a complicated, recovery. The abortive cases, epidemic or sporadic, are characteristic. Patients complain of headache, may vomit or have a convulsion, with high temperature; there is severe headache for a few days, with rigidity, and characteristic symptoms, ending in recovery, or the patient may be totally deaf. These are not uncommon, and are not generally recognized because their duration is so short.

Finally, the regular type is that in which a patient in apparent health is taken with sudden severe headache, vomiting, fever, and a rapid pulse. The vomiting may not persist beyond the initial stage, but the headache continues and increases, rigidity of the neck becomes apparent, and after a few days, opisthotonos may set in; stupor and coma develop, and the patient has the symptoms of the acute or subacute form.

Under the acute classical form we may include the cases which last from one to four weeks. The patients die or recover with or without complications. Under the chronic form we understand those cases which last from two to three or four months. The patients make a recovery with sequelæ or complications, or die of exhaustion.

The Mode of Onset.—In the vast majority the main characteristic of the onset is that it is sudden and abrupt. Patients in apparent excellent health are stricken with the disease. There is a history of gradual onset in a very small percentage of cases, and the writer believes that in these there may have been a previous indisposition to alter the history of the onset. In this respect this form of meningitis differs from the secondary forms, especially the tuberculous, in which the onset is usually gradual.

When fully developed the clinical features are quite characteristic. The patient lies in a semiconscious, stuporous, delirious, or comatose condition. The position most affected by the patient in bed is that on the side in the crouching posture, the head retracted, the knees drawn up, the arms flexed, the hands supporting the chin. In some cases there may be an eruption on the body, either petechial, roseolar, or erythematous. There is generally high temperature which may at times fall to normal or subnormal. The patient may toss about in bed or lie, when undisturbed, in a muttering delirium, or, when disturbed, show signs of hyperesthesia.

Another clinical type which occurs both sporadically and in epidemics is that which affects children below two years of age. It is the so-called posterior basic type of meningitis, which has been described by Gee and Still under the title, at first, of cervical opisthotonos and later, by Still, under the title here given. In these cases the meningitis confines itself to the structures at the base of the brain, from the optic chiasm backward to the pons and cerebellum. These cases are for the most part fatal, developing hydrocephalus in course of time, but in exceptional cases resulting in recovery.

The so-called tâche cérébrale is present. When an attempt is made to straighten the neck there are evidences of extreme pain. If the pupils are closely watched during this procedure distinct mydriasis can be seen. In children close observation of the eye reveals an automatic oscillation to and fro on the horizontal axis. The pupils may be contracted or dilated, according to the stage of the disease. When the patients are suffering pain the pupils are seen to dilate. The pulse in the acute cases is rapid, at times irregular, but latterly becomes slow. The respirations may be sighing, shallow, sometimes imperceptible, but rarely of the Cheyne-Stokes variety.

The patient may not only resist any interference but all nourishment. In some cases there are intervals of consciousness during which the patients complain of intense headache, usually of the occipital, sometimes of the frontal type, and sometimes of pain along the spine. Some complain of abdominal pain. After a varying length of time the patients may regain consciousness and gradually improve, but the last thing to disappear before convalescence is the rigidity of the neck and the contractures of the limbs. As convalescence approaches there may be

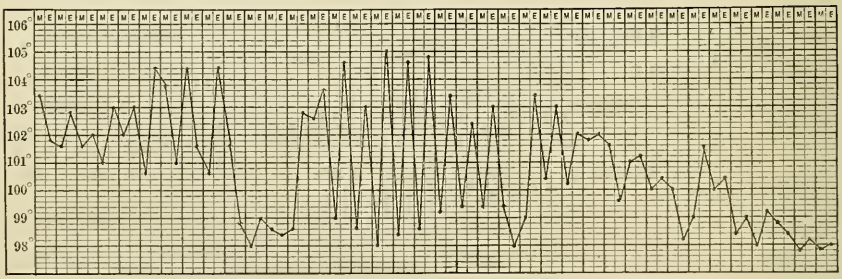
intervals during which the patient complains of headache and the temperature rises, and intervals in which he is quite comfortable; or he may regain consciousness or pass into deep coma, from which he never rouses, having progressive retraction of the head, emaciation, and coma.

In other cases patients pass into a chronic stage during which some of the symptoms, such as stupor and delirium, may abate. The fever continues, over a period of weeks, with intervals of headache and pains in the limbs, especially along the sciatic nerves. In some of these cases emaciation is marked. Recovery from this may occur gradually.

Individual Symptoms.—Fever.—The temperature is not characteristic. In some cases it is decidedly irregular, more especially when the duration is short. Cases of a week's duration will show a gradual rise from the onset to a certain point and then a gradual decline. In this respect the temperature curve is no more characteristic than that seen in typhoid fever of short duration. In other cases the fever curve is exceedingly irregular and may extend over a week, with remissions and intermissions; that is, the temperature may drop a degree or two, or at times to normal or subnormal, and mount again to its original height or a degree or two lower.

In another class of cases the fever seems to take a distinctly intermittent course and these, it seems, are the cases which have been mistaken either for malarial fever or typhoid in the later stage. The temperature makes exceedingly wide excursions and may mount on the same day to 105° or 106° F. and drop within a few hours to normal or subnormal, to return within a few hours to its original height. Such a temperature may continue for weeks, and in this respect, if combined with other symptoms of cerebrospinal meningitis, must be regarded as characteristic of this set of cases.

FIG. 11



Temperature curve showing irregularity and wide excursions.

In the subacute or chronic forms, especially those occurring in children below two years of age, the temperature after a time may drop to normal and continue normal for weeks or at most half a degree or a degree above it, in this respect simulating very closely the fever in tuberculous meningitis. In older children and in adults the temperature in the subacute period may also drop to the normal and after some days mount again. The temperature does not seem to be dependent on bacterial reinvasion or exacerbation of the symptoms in these subacute and chronic

cases. The patient appears to be in much the same condition, with the exception of the temperature falling to normal and remaining there for days, mounting again in irregular fashion.

During convalescence a patient who has been doing fairly well may suddenly develop an intermittent form of fever. In these cases at times we have with this temperature a slight return of the former symptoms, such as headache and at times vomiting. These seem to be more in the nature of a relapse. In some of these cases, apparent convalescence may be interrupted by a week or two of recurrent fever which finally disappears, with complete recovery of the patient.

Pulse.—The pulse is, as a rule, rapid. It may range from 90 to 120 in the course of twenty-four hours and is irregular both in rhythm and force. This irregularity may be said to be characteristic of these cases.

Respiration.—The respirations may be irregular, sighing, superficial, or deep. As a rule the rate is increased in frequency to a varying extent. The Cheyne-Stokes respiration is not as common as in the tuberculous form of meningitis, but the irregular sighing form is very common.

Skin.—The eruptions vary according to the nature of the epidemic and the severity of the infection. In severe cases, petechial eruptions and hemorrhages under the skin are quite common in certain epidemics. The petechiæ may be so small as to be scarcely seen, or in some cases, especially in young children, the ecchymosis may cover areas as large as the palm of the hand, particularly in the acute malignant forms. A roseola like that in typhoid fever is not uncommon. Erythematous eruptions are quite common at the outset of the disease and give way to petechial forms. This is seen especially in children in whom an erythema may usher in the primary symptoms, to disappear in a few hours and be followed by a petechial eruption. Herpes are seen on the lips, alæ nasi, and different parts of the body. The writer has seen extensive herpes with bleb formation on one hand. These herpetic eruptions have nothing characteristic as to location. They are not pathognomonic. In some cases the herpes may be distinctly hemorrhagic.

Mental Condition.—It may be said in a general way that at the outset the intense headache gives way to sopor and subsequently to stupor. There is delirium of a mild type at first which may become noisy later on. If such patients are spoken to, however, they rouse from their stuporous condition and answer questions quite intelligently provided that the auditory apparatus has not been affected. In some cases there is distinct deafness, in which event it is impossible to come to any definite conclusion as to the mental state. In the acute cases which take a favorable course the patients come out of their delirious condition very much as in pneumonia and are quite rational, remaining so until the termination of convalescence, though other symptoms referable to the nervous system, such as rigidity, opisthotonos, and Kernig's sign may persist. In some cases the mental condition passes through the various stages of sopor, stupor, and coma. In others, after having passed through the primary stage of stupor and recovered partial consciousness, convalescence is marred by a mental condition closely

simulating idiocy. In this state the patient may continue for an indefinite time, finally returning to the normal condition or remaining idiotic.

The Nose and Throat—In a large number of children in the epidemic of 1904–05 a coryza was present at the outset. In many cases this with conjunctivitis caused some confusion with measles. In quite a number of cases the tonsils and pharynx were markedly inflamed. Many chi dren suffer from adenoids, and a nasal discharge from such causes must not be confused with the acute coryza.

The Eyes.—Contrary to the generally accepted opinion we have found that examination of the fundus oculi in the majority of cases reveals no change in the optic papilla, although in quite a number there was dilatation of the veins and congestion without neuritis. In some cases there may be descending neuritis. In a group of 26 cases of meningitis of the tuberculous type neuritis was found in fully 77 per cent. It was either optic neuritis or papillitis with or without the presence of tubercles in the choroid. In those cases of cerebrospinal meningitis which recover, the damage to the eyesight varies in different epidemics. Blindness or definite changes in the fundus in those patients who have recovered in the recent epidemics in New York have been uncommon, although records of such cases are found elsewhere. In the fatal cases an extension of the inflammation along the optic nerve has been described. These changes may involve not only the nerve but the choroid, the vitreous, and the structures of the globe. In various epidemics much confusion has been caused by records of eye lesions which evidently were not due to meningitis of the diplococcus type. In the epidemic of 1904–05 the writer saw many children in whom conjunctivitis was present, due apparently to affection of the nerves of sensation and loss of protection to the conjunctiva. The lesion is one of the fifth nerve. Other forms of conjunctivitis are due to the direct action of the *Diplococcus meningitidis*. Keratitis is due to affection of the fifth nerve by direct extension (Councilman). The nerves of the muscular apparatus of the eyeball may be affected; thus paralysis of the abductor or oculomotor nerves may result. As to the simple absence or presence even of photophobia it is not possible to come to a definite conclusion. In this disease there is great hyperesthesia and in some subjects this extends to the conjunctiva. The patients may lie with the eyes closed tightly and resist all attempts to open the lids.

The Ear.—The ear is more commonly involved in young subjects than in those later in life. In the majority of cases there is some redness of the drum. The younger the child the more apt is this to be the case. There may be otitis, with the formation of pus in which is found the *Diplococcus intracellularis*. There is no case on record in which it has been proved that the disease was inaugurated by extension of primary inflammation of the ear to the meninges. In many patients who have recovered there is permanent deafness. This may complicate attacks which have been exceedingly mild and only lasted at the most a week, with complete recovery otherwise. In young children this complication may occur at the earliest stage, and is due to inflammation of the auditory nerve. Moos found that of 64 cases of meningitis fully 57 per cent. of

those who recovered were deaf. Deafness may appear as early as the first day of the disease and as late as the fourth month of convalescence. It is possible that the abortive form of cerebrospinal meningitis is in many cases the direct cause of deafness.

The Blood.—In all cases there is a leukocytosis at the outset. This is of the polynuclear type and ranges from 20,000 to 55,000 to the cmm. exceeding 25,000 in fully 55 per cent. of cases. The lowest leukocyte count personally observed has been 11,000 to 12,000. In the chronic form the leukocyte count may drop to normal and remain there for some length of time, in this way closely simulating what is seen in forms of tuberculous meningitis. So far as the chronic forms of cerebrospinal meningitis are concerned the leukocyte count is of no clinical value.

In the so-called basic cases in infants and children, the leukocyte count may range from 32,000 to 34,000, but toward the close of the disease when the temperature rises above normal it may fall as low as 9000 to 10,000, in this latter respect resembling tuberculous meningitis. The majority of these do not recover, and are complicated with permanent hydrocephalus. In the fatal cases in which fluid obtained by lumbar puncture is quite turbid or purulent the leukocyte count may be as high as 35,000 to 55,000, while in other fatal cases with a thick, turbid fluid obtained by lumbar puncture it will not exceed 23,000. Patients who have recovered showed a leukocyte count varying from 14,000 to 28,000, whereas during the course the count may have mounted to as high as 45,000 even on the twenty-first day of the disease. The prognosis cannot be made by the leukocyte count alone.

Kidneys.—In many cases there are evidences of a mild form of parenchymatous nephritis. There may be slight traces of albumin and a few casts. In some instances at the outset there is blood in the urine, with casts and albumin. These are patients in whom the petechiæ are prominent. In a large percentage there are no renal symptoms.

Convulsions.—These are especially frequent at the onset, particularly in infants. As a rule they are not so frequent as in disease of the convexity of the brain alone or in leptomeningitis from various causes. In children the convulsions are not often repeated after the initial stage. Convulsions occurring in the course are of serious moment and point either to distension of the lateral ventricles of the brain or to pressure of fluid in the subarachnoid space both at the base and convexity.

Convulsions may supervene in patients who are apparently on the way to recovery. The temperature has begun to fall and is low. The pupils may be dilated and there is a stupor. In these there may be signs of fluid in the ventricles. Convulsions in these patients are repeated daily and should warn us to intervene before a fatal issue. *Rigors* of a severe type may occur in the course of cases of an acute type. In such the exudate is slightly or markedly purulent.

Kernig's Sign.—This consists in an inability to extend the leg fully when the thigh is placed at right angles to the trunk. Kernig observed this sign when he attempted to sit the patient at the edge of the bed and straighten the legs. Osler simplified the sign by showing that it

may be elicited with the patient in the recumbent posture by placing the thigh at right angles to the trunk and then attempting to extend the leg on the thigh. Kernig not only found this sign in meningitis and considered it pathognomonic, but he observed it in the convalescence from the disease when the patient was up and walking about. These observations have been confirmed with reservations. Kernig's sign is not pathognomonic of meningitis any more than rigidity of the neck. It is, however, very valuable and completes the picture of the disease. It is present in diseases of the most diverse nature in which cerebral symptoms are present and toxemia is great.

It is important to recognize what is and what is not the Kernig sign, especially in meningitis. In some cases an attempt to straighten the leg on the thigh will be resisted at an angle of 135° and in others at an angle of 90°. It is therefore but fair to Kernig to include his sign between these two variations. Unfortunately this sign may be absent in malignant forms of cerebrospinal meningitis, especially in those with collapse symptoms. In these patients the Kernig sign may be absent, although it may reappear on a subsequent day. It may be absent at the onset of an ordinary attack and appear after the disease has lasted a day or two. It is present in the majority at some time in the course but may not be present at critical periods.

When Kernig's sign is present and an attempt is made to straighten the limb against resistance, there is intense pain, and a simulation of the Babinski reflex occurs at the time of the attempt to straighten the leg on the thigh against this resistance.

During convalescence when the temperature remains normal for a variable length of time, the Kernig sign gradually loses its intensity, and as convalescence is established, as a rule, it completely disappears.

The cause of Kernig's sign has been a matter of much discussion. Roglet submits two causes. First, that it may be due to intraventricular pressure. This theory is supported by the fact, which the writer has confirmed, that the Kernig sign is not as marked after as before lumbar puncture. On the other hand, excessive ventricular pressure has, in the cases of collapse above mentioned, resulted in an entire disappearance of the sign. Another explanation is that the posterior spinal nerves are in a constant state of irritability and that there is, therefore, persistent tonic shortening of the muscular fiber which cannot completely straighten, and when an attempt is made to do so there is resistance.

The Kernig sign is present in other forms of meningitis, but in tuberculous meningitis, especially in children, its presence is not so constant and in the cases studied by the writer it was absent in fully one-third. It is not to be relied on in very young infants in whom there is a muscular tonicity of both upper and lower extremities which is normal and becomes exaggerated on the onset of the least illness. Its occurrence in children below two years of age is variable for reasons which the writer cannot explain.

Babinski Reflex.—This is inconstant in cerebrospinal meningitis, having been present in only 4 out of 25 cases, whereas in tuberculous cases its presence is more frequent, being absent in only 6 of 26 cases.

Therefore, though it may not be of value as a positive sign, its absence may be considered in the decision as to the nature of a meningitis.

Brudzinski's Collateral Reflex.—This is an exceedingly useful reflex found in meningitis and cerebral disease, and described by Brudzinski in 1908. It consists, first, in a flexion of the opposite leg, if passive flexion is made on one side; this is called the "identical collateral reflex." Sometimes this movement of the opposite leg is "extension" instead of "flexion;" it is then called "reciprocal collateral reflex." A more useful sign—and one strongly presumptive of meningitis of any variety—was described by Brudzinski in 1909, the so-called, "neck sign." As the patient lies prone on the back the head is flexed on the chest with one hand and the chest steadied with the other. There is a resultant flexion of the thighs on the pelvis and the legs on the thighs. If present this sign is strong presumptive evidence of meningitis, more so than the Kernig sign. It is found in meningitis at all stages.

The Skin and Tendon Reflexes.—In the majority of cases the skin and tendon reflexes are present in the early stages, but are apt to disappear in the rapidly malignant and fatal type, and in moribund cases.

Hyperesthesia and Mental Irritability.—Very frequently, after the symptoms have set in, the patients are irritable, refuse to be comforted, start at the least sound, and lie on the side, this being most comfortable on account of the flexion of the arms, legs, and trunk. Any attempt to disturb the patient is met with resistance. This is in marked contrast with other forms, especially the tuberculous, in which reaction to irritation is rather exceptional.

Facial Paresis.—This is present in those forms, both in adults and in children, in which either at the outset or in the course the exudate and pressure symptoms are most pronounced at the base of the brain. During the epidemic of 1904–05 these were not uncommon and simulated tuberculous meningitis with the exception that in the latter disease pareses are apt to supervene late in the affection, whereas in epidemic cerebrospinal meningitis pareses may supervene early in the course.

The grave significance of the facial paresis or paralysis in tuberculous meningitis cannot be applied to epidemic cerebrospinal meningitis, for they may disappear in the latter affection with convalescence.

Rigidity of the Neck.—Great stress has been laid on the presence or absence of rigidity of the neck both in adults and children as a pathognomonic sign in cerebrospinal meningitis. In those patients in whom the onset is foudroyant and in whom collapse occurs at the outset, neck rigidity, as well as Kernig's sign, may be absent. If the patient lives long enough to withstand the shock of the onset the rigidity may appear later with the Kernig sign. As a rule, neck rigidity is present in most cases either of mild or of marked severity, and with it there is mild or marked opisthotonos. It is in the posterior basic forms in young children that the rigidity and opisthotonos reach the height of development. According to Osler, rigidity of the neck is not usually present in the pneumococcus meningitis, but the writer has seen one patient in whom rigidity was present with opisthotonos. The rigidity and opisthotonos are so marked either early or in the course of the disease that

any attempt to straighten the neck of the patient not only meets with resistance but causes pain. If at this time we observe the pupils we will see evidence of irritation, possibly of the sympathetic, as shown by marked dilatation of the pupils. Mydriasis which supervenes in any attempt to straighten the head is a most valuable sign that the neck rigidity is due to irritation of the cervical nerve roots and thereby also the sympathetic fibers. This mydriasis is useful in differentiating rigidity of this kind from that which we so frequently find in gastro-enteritis and pneumonia in children.

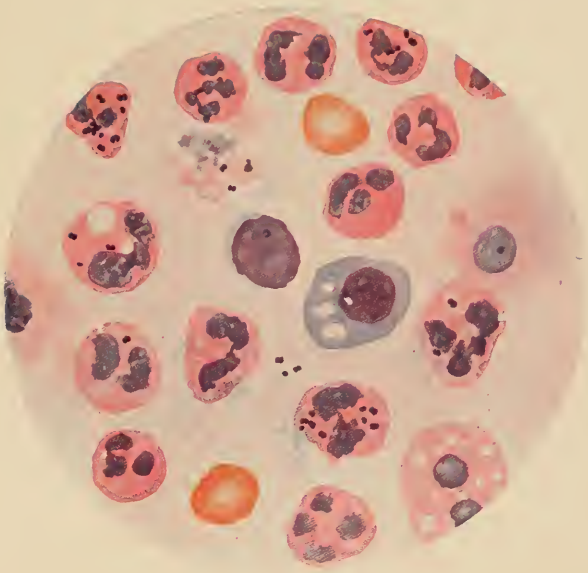
Macewan's Sign.—Macewan has pointed out that in various forms of meningitis in children, especially of the tuberculous type, we obtain a hollow note on percussion over the anterior horn of the ventricle. That is, if the patient is caused to assume the upright position with the head inclined to one side, percussion of the inferior frontal or parietal bone will give a tympanitic note. This more frequently obtains in tuberculous meningitis than in epidemic cerebrospinal meningitis.

In those cases of epidemic cerebrospinal meningitis in which hydrocephalus supervenes, both in younger and older children, the author has found that this hollow note is a very important guide to the presence of fluid in the ventricle. In cases of chronic hydrocephalus with increase of fluid in the ventricles a marked Macewan sign is always present. In a child below two years of age if there is marked rachitis a tympanitic note may be obtained in the manner described; such cases must be excluded in eliciting this sign in the study of cerebrospinal meningitis.

Lumbar Puncture.—The fluid obtained by lumbar puncture has been variously described and an attempt made to trace the connection between its physical characteristics and the course, duration, and prognosis of the disease. The writer cannot agree with those views which take the physical characteristics of the puncture fluid as support for any of these data. At the outset the fluid may be quite turbid and purulent and the patients make a good recovery. The fluid at this time may be quite clear and the ultimate result just the contrary. A fluid which has been turbid at first may clear up subsequently, become quite clear, and after a week or two may again become turbid. An attempt has been made to explain the turbidity by reinvasion and regeneration of the micro-organism. It certainly demonstrates a diminished resistance of the body to the invasion of the disease. In chronic or subacute cases of long duration, especially in children, the fluid finally becomes clear, and may be devoid of microörganisms or contain them in such sparse numbers as to be discovered only by the most painstaking measures.

The cytology of the fluid obtained by lumbar puncture is of great interest. It shows a preponderance of polynuclear leukocytes in a great majority of cases, the mononuclear leukocytes being present but in much diminished numbers. In a few cases seen by the writer, however, there were mononuclear elements present to a preponderating degree. (Plate X.) These are cases which have lasted some time and in which the disease has come to a standstill so far as active inflammatory processes are concerned, as seen especially in the chronic posterior basic cases, in which hydrocephalus has supervened. Here the mononuclear

PLATE X.



Cover-glass Stain of the Sedimented Fluid Obtained by Lumbar Puncture in Epidemic Cerebrospinal Meningitis.

Polymorphonuclear cytology; vacuolization of the leukocytes and lymphocytes; peculiar conformation of the nuclei in cells; large cells resembling lymphocytes; Diplococcus meningitidis in the cell body of the leukocytes and also outside of the cell bodies in smaller numbers

cells predominate as in tuberculous meningitis. Bendix explains this by the fact that in chronic cases there is no longer an exudate but a transudate In acute cases a preponderance of polynuclear leukocytes is strong evidence against tuberculous meningitis.

In the puncture fluid we find the *Diplococcus meningitidis intracellularis* in the polynuclear leukocytes. It is situated mostly in the cell, in some instances seeming to pack the cell quite full, and in very rare cases it is found outside the cell body. Its presence or absence in the puncture fluid may not have any connection whatever with the clinical course, but be rather a matter of filtering through the fibrinous exudate. The writer has found the diplococcus a few hours after the onset and as late as the fifteenth week. In cases which have lasted over a few months it frequently disappears from the puncture fluid and is very difficult to demonstrate either by culture or cover-glass spread.

In those cases in which the puncture fluid does not contain the diplococci or tubercle bacilli we may conclude rather in favor of the epidemic than the tuberculous type. The writer's experience substantiates the view that the presence of tubercle bacilli in the puncture fluid of tuberculoid meningitis is quite constant and their detection depends very much upon patience and technique.

In addition we find in the puncture fluid of epidemic cerebrospinal meningitis, mononuclear lymphocytes, with large nuclei, and a thin pale staining zone of cell body. Vacuolization of the leukocytes is not uncommon. In the polynuclear leukocytes the nuclei are irregular in shape and in various stages of division.

Complications and Sequelæ.—The Eye.—In those patients who have recovered in the epidemics seen by the writer there have been few instances of blindness or severe injury to the eyesight. In fatal cases there have been a few in which panophthalmitis, with destruction of the globe, resulted.

The Ear.—Otitis in its various forms is a very frequent complication. In fact, in certain forms of the affection, especially in young children, English observers have advised early puncture of the drum even with slight symptoms of myringitis as a possible measure of relief. The otitis may be catarrhal or purulent and with or without mastoid complication, the latter being infrequent. The ear infections seem to be in direct extension from the brain, or an independent infection from the nose and throat. In quite a number of patients at the very outset or in the course, deafness supervenes without any lesion of the middle ear. In these there seems to be an affection of the auditory nerve. Some of these may improve, others remain permanently deaf.

The Skin.—Skin eruptions may scarcely be considered as complications, though subcutaneous abscesses have been mentioned, in some of which the diplococcus has been found.

Pericarditis.—Pericarditis may run its course without any physical signs, even though these be searched for. In pericarditis few adhesions are found and the amount of effusion is not large.

Pneumonia.—Pneumonia is not uncommon and may be caused by the *Diplococcus intracellularis* or by the pneumococcus. The course

of the disease is severer than in uncomplicated cases. The presence of pneumonia means a fatal issue and the same may be said of pericarditis.

Joint Complications.—Councilman, Mallory, and Wright record 6 cases of arthritis among 111 in the Boston epidemic. Osler described two cases in adults in whom the wrists, hands, elbows, knees, and other large and small joints, including the hip, were affected. The skin of the joints becomes red, brawny, and diffusely erythematous for several inches above and below the affected joints. Over one knee which was affected there were purplish blotches. The pus withdrawn from one joint showed the meningococcus, and in 1 case at least the arthritis seemed to be a sequence of a species of meningococcus septicemia, inasmuch as the meningococcus was isolated from the blood during life.

The joint manifestations may be among the first symptoms of the disease. During the epidemics of 1904 and 1905 the writer saw several cases of joint affection, and in one similar to that of Osler the arthritis seemed to be one of the first symptoms. In the cases in children the arthritis never resulted in suppuration. The symptoms resembled a mild attack of rheumatic fever. In Osler's cases, the joint affections were more serious and were a manifestation of general sepsis; 1 patient died, the other, having begun with arthritis and fever, developed paraplegia and other serious symptoms.

Hydrocephalus.—Among the interesting conditions met with in convalescence are those in which the disease having run a moderately severe or mild course, the temperature having been normal for days and the patient apparently doing well, the mental condition becomes clouded. It is noticed that such patients no longer give attention to what is said to them and do not ask for nourishment. The pulse, having been slow, becomes more frequent, the temperature may rise, the pupils become dilated, there is a stupid stare, and the patients sleep most of the time. Percussion over the site of the horn of the ventricle as described by Macewan gives a hollow tympanitic note early in the condition. In such cases an accumulation has taken place in the ventricles of the brain and hydrocephalus has supervened. When this is relieved by lumbar puncture the patients seem to arouse themselves, the pupils return to normal size, the intelligence is awakened, as it were, but relapse may occur after several days, necessitating further interference. Such patients may make a good recovery, pass into a state of chronic hydrocephalus with idiocy, or a sudden fatal termination may occur. In many of these patients there are intervening convulsions which cease on the relief of intraventricular pressure by lumbar puncture.

Relapses.—The frequency of relapses has been studied by Flexner and Jobling. Of 400 cases there is a record of undoubted relapses in 19 cases, 14 of which recovered.

Mortality and Prognosis.—The mortality varies with the virulence of the epidemic and the age of the patient. The death rate, before the treatment of the cases by serum injections, fluctuated in various epidemics from 90 to 25 per cent, the average being 75 per cent (Flexner). In an analysis by Flexner of 1300 cases treated by serum all over the

world, and principally in America, grouping all ages, there was a mortality of 30 per cent. The mortality was lowest in cases injected early in the disease; 119 cases injected in the first three days of the disease had a mortality of 18 per cent.; 346 cases injected from the fourth to the seventh day a mortality of 27 per cent.; and 666 cases injected later than this a mortality of 36 per cent. The mortality is greater in infants under one year of age. Of 125 infants below one year of age 63 died and 62 recovered. Of 16 infants injected in the first three days of the disease 12 recovered. Flexner concludes that the age from two to five years is most favorable to recovery, the mortality in 200 cases being 15 per cent. The writer has always felt that from five to ten years was the most favorable period.

Prognosis is closely allied to the question of permanent cure. In the statistics mentioned "cure" must mean simply the immediate results of treatment. The patients did not die, but recovered and were apparently well. But in all such cases we cannot be certain but that in time mental defects, or sequelæ, may develop, and this is most noticeable in children below two years of age. While we can speak of "cure" as a result of treatment we cannot, as yet, give statistics as to absolute *restitutio ad integram* of the individual in mental and physical strength.

Diagnosis.—This would seem to be quite a simple matter in the majority of cases, and such it is. The only other diseases which very closely simulate this affection are pneumonia, the cerebral forms of typhoid fever, other forms of meningitis, and acute polio-encephalitis.

In epidemic cerebrospinal meningitis the onset is sudden in the vast majority and the patient is in apparent health when attacked. The onset is with fever, headache, and vomiting. In children convulsions are not uncommon. In an epidemic an adult will suddenly fall prostrate; or he may complain of slight headache and then become unconscious or have convulsions. In these cases the diagnosis is clear. In children, however, the onset occurring as it does in a great number of cases with symptoms referable to the gastro-intestinal tract, such as vomiting, diarrhœa, fever, and abdominal pain, is not so suggestive. Conditions simulating very closely a mild attack of gastritis, which in twenty-four hours pass into collapse without any previous warning, are confusing. The pallor and the shock of the collapsed condition seem remarkable in view of the fact that the child may have been playing a few minutes previously. In such cases there are always evidences of some systemic infection and we may find a few purpuric spots. The disease may have a sudden onset with symptoms of gastro-enteritis and without rigidity or Kernig's sign. The cytology of fluids obtained by lumbar puncture is of decisive importance as is also their bacteriology.

The cerebral symptoms in some forms of typhoid fever which have their onset in an acute, abrupt manner have to be considered. The history is important and examination of the blood both for the Widal reaction and for the presence or absence of leukocytosis will aid in the diagnosis. An enlarged spleen may be present in cerebrospinal meningitis as well as in typhoid fever.

Cerebrospinal meningitis may be confounded with an ordinary attack

of influenza or otitis. The ears should a'ways be examined in doubtful cases or in unconscious patients with an unsatisfactory clinical history.

This form may be confounded with tuberculous meningitis or with that due to other causes. The pneumococcus meningitis may resemble it, although meningitis due to ear trouble fails to simulate the epidemic form in some of its most salient features, such as the onset, rigidity, and opisthotonos. Some forms of streptococcus meningitis run their course without revealing any symptoms referable to the cerebrum until near the close, when a subdural collection of pus and a localized meningitis may become general. In such cases there is usually a history of previous ear trouble.

The tuberculous form may, in exceptional cases, simulate epidemic cerebrospinal meningitis. In tuberculous meningitis the onset is usually insidious. There is a prodromal period of at least a week or two in which the patient complains of indefinite malaise and in which symptoms are cumulative up to a certain period, after which they become pronounced. The leukocytes in tuberculous meningitis rarely mount above 20,000 to the cmm. except in the premortal stage, whereas in epidemic cerebrospinal meningitis they are higher. In tuberculous meningitis the absence of reaction on the part of the patient to interference, the absence of hyperesthesia, of neck rigidity, as seen in cerebrospinal meningitis, of opisthotonos, both in children and in adults, aid in coming to a definite conclusion. The pareses seen in tuberculous meningitis referable to the affection of the cranial nerves at the base of the brain come on, as a rule, late in the affection, whereas in cerebrospinal meningitis they may be present at the onset or during the course. An examination of the fundus oculi may reveal choroid tubercles.

Polio-encephalitis or Encephalitis.—This may at first closely simulate cerebrospinal meningitis. A patient, in previous good health, is suddenly seized with fever, headache, and vomiting; there is sopor which gradually deepens; the fever may gradually drop to the normal but the sopor continues; the patient is delirious, there is hyperesthesia, pain in the nape of the neck, marked rigidity, and the Kernig—or even Brudzinski's—sign, with evidence of mild hydrocephalus (Macewan). Close examination will invariably reveal a drop from the first high temperature to the normal, and a basilar palsy such as that of the muscles of the eyes or face. In all cases a lumbar puncture will clear the diagnosis. In the puncture fluid of polio-encephalitis there are no bacteria; it is clear and there is a preponderance of mononuclear lymphocytes, in some cases as high as 100 per cent. This excludes a purulent process.

Indications for Puncture.—Lumbar puncture is imperative in all cases in which there is a suspicion of meningitis. It is indicated in those cases of sudden onset with symptoms of complete collapse; in these the collapse seems to be due to intraventricular pressure. When lumbar puncture is made twenty-four hours after the onset, after such a period of collapse as has been described, the fluid sometimes spurts several feet.

Lumbar puncture is indicated also in those cases in which headache and delirium are excessive. The patient complains of constant headache, has retraction of the head, opisthotonos, and high fever. In such

cases the intraventricular pressure seems to be great. In those cases in which, during convalescence, the patient suddenly develops symptoms of hydrocephalus, such as convulsions and stupor, dilatation of the pupils and subnormal temperature followed by a slight rise, and slow pulse followed by an increased rate, puncture should be done immediately and repeated at short intervals.

In meningitis, the first result of intracranial pressure is an acute, subacute, or chronic distension of the ventricles of the brain with fluid, and it is the early detection of this fluid which gives the absolute indication to relieve distension by lumbar puncture. The mode of detecting acute hydrocephalus, whether caused by acute distension of the ventricles on the first day of a cerebrospinal meningitis, or during the slow onset of a tuberculous meningitis, is by percussion of the skull. The writer considers this the only definite means of determining whether there is an increase of fluid in the ventricles or the subarachnoid space causing pressure effects. Lumbar puncture, except in the newborn, is devoid of danger and should be performed without delay in all cases in which we have reason to suspect meningitis. I have excepted the newborn because in two of my cases of meningitis in the newborn—one an infant ten days old, another eight weeks of age—in which there was a purulent fluid obtained by lumbar puncture, both infants died during the puncture from fatal apnœa. This possibility should always be borne in mind even in older children, though in the latter it is of only occasional occurrence. Repeated rises of temperature are an indication for repetition of puncture. The aim, especially in young infants and children, is to puncture early, as in these cases delay means irreparable ventricular pressure and rapid advance of the disease. In some young infants even early puncture reveals a closure of the canal of Magendie, due to to rapid accumulation at the base of the brain of inflammatory products.

Treatment.—This divides itself into the specific treatment, that with the Flexner serum, and the symptomatic and dietetic management.

The specific treatment consists in the introduction into the subarachnoid space and the spinal canal of the serum which has been perfected by Flexner. This serum differs in its action materially from sera used in other infectious diseases, such as diphtheria, in that it must be so placed as to come in contact directly with the etiological organism.

The first effect of the introduction of this serum is striking. The subarachnoid fluid is markedly freed from microörganisms after having been filled with them, or they are diminished in number. The effect of this serum on the microörganisms is direct; it is really a bacteriolytic agent. The most brilliant results have been obtained in cases which have received the serum within the first twenty-four hours or few days of the disease. The earlier the serum is administered the more complete, even in young infants, is the result. There are, of course, among the unsuccessfully treated cases many which have recived the serum during the first twenty-four hours of the disease. The failure of success in such cases is explained by Flexner himself in that certain strains of meningococci are not reached by the serum.

Mode of Administration of the Serum.—The serum is warmed to the body temperature in a small beaker glass and held ready for injection. Lumbar puncture is performed and 30 cc. or more of the subarachnoid fluid removed and as much of the serum is then introduced. The serum being harmless it should be introduced in doubtful cases. When the primary lumbar puncture shows a clear fluid we should introduce the serum first and then wait for an examination of the fluid. In cases which show a turbid fluid on lumbar puncture it is best to repeat the injection of fluid in the following twenty-four hours. The method of introducing the serum is that advocated by Quincke. Gravity is alone used to force the fluid into the canal. After the subarachnoid fluid is withdrawn, the needle being *in situ*, the serum is introduced by means of a small glass funnel to which rubber tubing is attached. The funnel can be improvised from an ordinary test-tube drawn out into a narrow point to which is attached a rubber tubing, in turn attached directly, or by means of a small metal connection, to the puncture needle. It is essential that no more serum be introduced than the amount of fluid withdrawn, and above all else the introduction should be slow, a respiratory apnœa may result from rapid change of pressure in the cerebrospinal canal. A syringe should not be used to introduce serum. Sometimes one injection, or even two injections on two successive days, may suffice. As a rule three injections of serum on three successive days are necessary to effect a fall in the temperature. The main guide as to the efficiency of treatment is the sudden or gradual drop in temperature with an accompanying amelioration of symptoms. With these results the serum injections are discontinued. After the injection of the serum it is not ususual after the temperature has been normal for days to observe a sudden rise, due not to the disease but to the effect of the serum (serum disease). Eruptions of an urticarial type are not infrequent. But beyond this no ill effects of the serum on the body are noticeable. Flexner denies anaphylactic effects.

Serum Treatment and Sequelæ. The serum does not prevent deafness, blindness, nor mental impairment. In children below two years of age the most discouraging sequel is hydrocephalus, which may appear when the fever has dropped and the patient is apparently doing well. These cases are described under the heading of Posterior Basic Meningitis.

Symptomatic Treatment.—Restlessness and delirium are best relieved, if they continue after administration of the serum, by warm baths, as proposed by Cancetti. Patients tolerate a full bath at a temperature of 107° F. for five to ten minutes and fall asleep afterward Morphine, bromide of potassium, pyramidon, all have their use in the relief of pain and restlessness. Lately hexamethylenamine has been suggested; it has been found by the writer to allay restlessness, especially in younger children, but cannot be said to have any powerful curative effects. The bowels must be kept clear and for this calomel is best.

Nutrition.—One of the main effects noticed is that the general nutrition suffers from the very onset. A patient in the condition of unconsciousness and delirium can be fed only at irregular intervals and this in short periods of time. If unconscious it is sometimes necessary to feed by

gavage, which as a rule is performed three times during the twenty-four hours. The feeding will be still more difficult if there is vomiting, which usually does not seem to be caused by the ingestion of food, although food may be vomited when administered. In spite of vomiting it is well to insist on the continuous administration of liquid foods. If the patients are not unconscious, even though they have fever, we may give solid diet. In children the appetite is especially capricious, and unless we give the food in small quantities and at frequent intervals the patients literally starve themselves.

Fever.—The fever requires very little treatment. As a rule, the highest range of temperature lasts but an hour, sometimes even less, and there is a natural fall in the temperature.

During convalescence the patients are weak and complain of stiffness and pains in the extremities. In such cases hot baths and judicious massage are particularly useful. Rough handling is painful but gentle massage strengthens the patient and reduces the pain and stiffness.

The complications, such as those connected with the eye and ear, cannot, unfortunately, be relieved by any treatment. During convalescence some patients, especially children, have a peculiar gait. They are very unsteady and walk very much as do the subjects of Ménière's disease. This condition may improve and gradually disappear of its own accord. It is seen especially in patients who are completely or partially deaf, and in whom there has been no affection of the middle ear. The otologists hold out very little encouragement in these cases as to the ultimate return of hearing, but it sometimes returns to a certain extent without any treatment.

The joint affections are treated on general principles. If the joint is painful and swollen it may be wrapped in cotton moistened with methyl salicylate, and salicylate of sodium given. If there is suppuration surgical treatment is indicated.

POSTERIOR BASIC MENINGITIS

Posterior basic meningitis may be said to be the form which acute cerebrospinal meningitis of the epidemic type takes in children below two years of age. In these subjects the peculiar conformation of the brain at the base seems to predispose to the development of this symptom complex. It is not seen, as a rule, in older subjects, and for a time was thought to be a form of meningitis *sui generis*, due to various causes. It is evident from observations during epidemics of cerebrospinal meningitis and of sporadic cases that the same etiological factor obtains as in older subjects, and that the youth of the subject, the susceptibility of the tissues, and possibly the conformation of the parts, tend to the development of certain symptoms.

This form of meningitis was first described by Gee and Barlow in 1878. They collected 25 cases, and the essential feature of all was "the holding back of the head." In fact, they called the disease cervical opisthotonos. They laid stress on the fact that in other forms of menin-

gitis and in tuberculous meningitis this peculiar symptom of head retraction was only exceptional, whereas in this form it was a constant symptom. In some of their cases the onset was gradual, in others sudden. In those cases in which the onset was sudden the opisthotonos alone, or accompanied by fever, vomiting, and muscular rigidity, seemed to be characteristic. The associated symptoms included rigidity of the limbs and convulsions during the course, which was chronic and particularly fatal, as only three of their patients recovered.

Similar cases have been described by Carr, and Still called attention to this affection in 1898 in a report of the postmortem findings in 8 cases of the 49 that he had collected. In these 8 cases he discovered, either in the ventricles or in the fluid withdrawn from the subarachnoid space, the *Diplococcus intracellularis* of Weichselbaum, although at the time Still was not absolutely certain of the identity of his microörganism with that of Weichselbaum. Nuttall subsequently proved the identity of the two organisms.

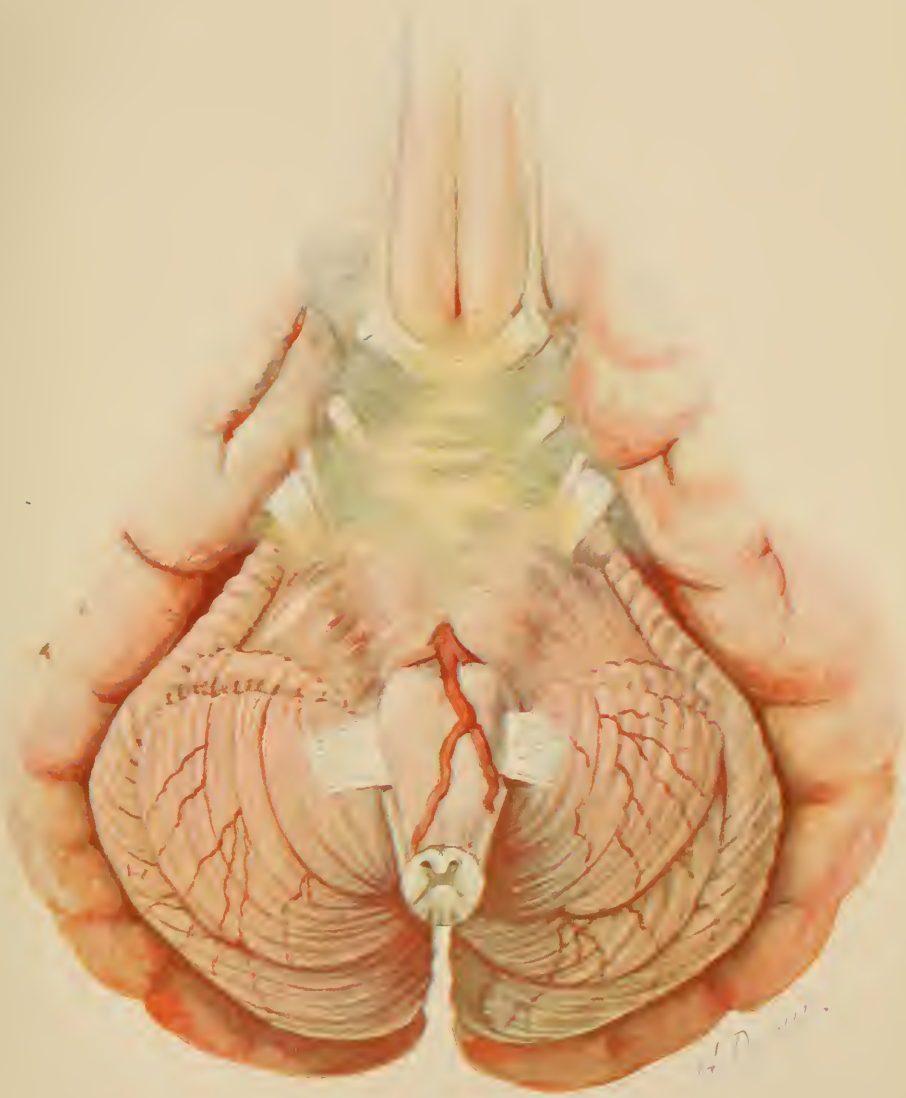
Morbid Anatomy.—The pathology has been clearly described by Gee and Barlow and by Still. The inflammation seems to limit itself to the posterior part of the base of the brain as the primary seat of inflammation in most cases. From this region the inflammation spreads down the cord to a varying degree, upward along the line of the ventricles, and forward along the base as far as the optic commissure and tips of the temporosphenoidal lobes; or the inflammation may begin in the transverse fissure and choroid plexuses. (Plate XI.) At an early stage the products of inflammation though circumscribed may be suppurative; later on they may become absorbed, but meningitis with adhesions results. These adhesions may unite the cerebellum and medulla, obliterate the foramen of Magendie and the fourth ventricle. In some the fluid found in the ventricles is clear, in others it contains flakes of fibrin and pus. In the latter cases the ependyma will be found to be thickened. The meningococcus may be recovered from the ventricular fluid.

In this form of meningitis there are few complications, whereas in 15 cases of suppurative meningitis there were complications such as pleurisy or necrosis of the petrous portion of the temporal bone. In some cases described by Still there was a mucopurulent secretion in the middle ear, but in none was there evidence of mastoid disease or extension to the brain or meninges.

In some of those cases which are fatal within six weeks, postmortem examination shows lymph at the base of the brain and cord. In those which die after three or four months there is hydrocephalus, with a thickening of the pia mater and arachnoid, with adhesions between the cerebellum and medulla and slight thickening of the pia covering the temporal or the temporosphenoidal lobes.

During the epidemics of cerebrospinal meningitis of 1904–05 the writer saw a number of children below two years of age in whom the disease took this peculiar form. Of 8 cases of posterior basic meningitis occurring during the epidemic of 1904 the ages ranged from four months to three years, and 1 was five years of age.

PLATE XI



Posterior Basic Meningitis. (Gee, Barlow, and Still.)
Author's case in an infant.

PLATE XII

Posterior Basic Meningitis. Characteristic position of the head and extremities. Child, aged fourteen months.

Symptoms.—The mode of onset, speaking only of cases below two years of age, which correspond accurately to the picture given by Gee, Barlow, and Still, was gradual in only one case. In the others the onset was sudden. The beginning of the disease may have simulated tonsillitis or an ordinary attack of gastro-enteritis, in that the child was taken with fever, vomiting, then with convulsions in some cases, and these convulsions may have been repeated daily for some weeks. After the disease had lasted for several days it was noticed that the head was retracted and the neck rigid. In other cases after the initial fever and vomiting the child became stupid and then the mother noticed that the fever continued and that the child was blind.

When fully developed the picture of the disease is quite characteristic. The children are somewhat emaciated, lie quietly, seldom crying out, the head is retracted, there is more or less opisthotonos, the upper and lower limbs may be adducted, the forearm flexed on the arm and the thighs on the abdomen, and the fingers flexed. In some cases they present the picture in the upper extremities seen in tetany. In other cases the lower extremities are extended and cannot be flexed, although the upper extremities may be strongly flexed. The foot may be strongly extended on the leg and the toes on the plantar surface of the foot, in this way resembling tetany. The body is bent backward, the head assuming an angle of nearly 90° with the spine. At times this opisthotonos and tetany relax and the spastic phenomena are not so apparent. (Plate XII.) As soon as disturbed, however, or if the surface of the back is rubbed, the patients assume the position of extreme opisthotonos. In others, in addition, there is a tendency to cross the legs. In some there are purposeless movements of the upper extremities in a sort of arc in front of the face. If the fontanelles are still open they bulge, and the sutures, in some cases in which hydrocephalus has supervened, are pressed apart by accumulation of fluid in the ventricles. In some cases there is strabismus. In all cases emaciation is extreme and the abdomen is retracted and rigid.

The temperature at first is raised two, three or four degrees above the normal. After some time the temperature may fall to normal or for days range between normal and one degree above normal, in this way simulating tuberculous meningitis. In others, after some weeks, without any apparent cause, the temperature will mount from normal to 106° F. and over and then fall to normal or subnormal daily, to rise again. These excursions do not last very long and seem to be due possibly to cerebral pressure, for after puncture there is not any new accession of diplococci in the puncture fluid. On the contrary in those cases the fluid was sterile.

The condition of the fundus of the eye is interesting. In most patients below two years of age there is no change in the fundus, no neuritis, contrary to what is seen in tuberculous cases in the majority of which there is change in the fundus. In all cases seen by the writer there was disturbance of the circulation, such as tâche cérébrale or evanescent erythema, due to vasomotor paresis. Kernig's sign is of very little value for the reason that the patients lie in the spastic or flexed position and

the thighs cannot be flexed on the abdomen. The so-called Babinski reflex is absent in most of these cases.

The Blood.—In most cases there is a leukocytosis ranging from 14,000 to 30,000. In many cases, however, the leukocytes may not mount above 10,000 to 14,000, in this way simulating tuberculous meningitis.

Of special interest is the character of the fluid obtained by lumbar puncture. In many acute or chronic cases it is not possible to obtain fluid by lumbar puncture, inasmuch as the canal of Magendie may be closed by adhesions. In those in which fluid is obtained it is found to be sterile in some instances, while in others it contains the *Diplococcus intracellularis*. Although in most cases the diplococcus may be found at the outset of the disease, later on it seems to disappear from the fluid or be present in very small numbers. Although the fluid may show a preponderance of polynuclear leukocytes later on when hydrocephalus supervenes mononuclear leukocytes may predominate.

The cause of hydrocephalus in posterior basic meningitis has been the subject of much discussion. It has been contended by English writers that a narrowing of the canal of Magendie, with an accumulation of fluid in the ventricles and their consequent dilatation, results in a permanent transudate in this locality. This, however, would not explain the great number of cases in which hydrocephalus exists with a patent canal of Magendie. Another explanation is that the vessels of the plexus of Galen becoming thrombosed, their walls thickened and inflamed, and circulation is retarded, thus causing a transudate into the ventricles.

Neither of these theories explains the particular symptoms in posterior basic meningitis. Given a child below two years of age attacked by cerebrospinal meningitis we still are at a loss to explain why, in the majority of cases, hydrocephalus follows. Aside from the cases of posterior basic meningitis, whose etiology has been dilated upon, the author has been fortunate in encountering a case of purely basic meningitis, posterior in type, in which the etiology was not that of the diplococcus of Weichselbaum but a pure streptococcus complicating a pneumonia.

Thus there are two forms of basic meningitis: First, primary, caused by the *Diplococcus intracellularis* of Weichselbaum and either epidemic or sporadic. This is the type of the disease described by Still. The second form occurs in older children and the symptoms in no way resemble those described by Still. There is no drawing back of the head, or opisthotonos; the symptoms are obscure until near the close. The characteristic symptoms of the first form are absent, but in addition to the stupor and symptoms of meningeal involvement we have, late in the disease, facial pareses, paralysis of the ocular muscles, slight rigidity of the neck, and Kernig's sign pointing toward involvement of the brain, especially at the base.

The author wishes to emphasize that the cases of posterior basic meningitis of the type described by Gee, Barlow, Lees, and Still may occur in epidemics and are due to the same essential cause as the form of the disease in older children and adults. In fact, it would appear that in the majority of children attacked by cerebrospinal meningitis below the age of two years the disease takes this form.

Treatment.—It has been proposed to interfere surgically. The skull having been trephined, one horn of the ventricle is opened and a drain of catgut is fixed in it, connecting this with the subarachnoid space, thus making the ventricular and subarachnoid spaces one. Pressure can thus be relieved by a general outflow of fluid. We have no statistics as yet of the success of this but it is difficult to see how anything else than the substitution of an external for an internal hydrocephalus is attained. In 8 successive cases the writer has performed ventricular puncture; that is, one or both ventricles of the brain were punctured, fluid withdrawn, and Flexner serum introduced. This was performed both early and late in the disease. In none of these cases did any improvement result. These ventricular punctures were performed in cases in which the lumbar puncture was ineffective, due to a closing off of the subarachnoid space. In the ventricles punctured the menigococcus was found in the ventricular fluid.

German authors (Bôkai) have published several cases of apparent cure of hydrocephalis following meningitis (posterior basic) by repeated lumbar puncture, extending over the prolonged periods, such as six months or a year. The writer has never succeeded in attaining any results by this method when hydrocephalus has once been established.

The treatment is most unsatisfactory. In a child below two years of age the prognosis of meningitis itself is bad; if, added to this, the disease is progressive, we know of no remedy which will stay its course. It has appeared to the writer that in these cases lumbar puncture would attain its ideal as a palliative measure if instituted early enough and repeated often. Its utilization must be directed especially to the prevention of the subsequent hydrocephalus, which seems hopeless when once established. Therefore, although a patient is apparently doing well, we should not hesitate to puncture repeatedly in order that intraventricular pressure may not permanently dilate the ventricles. The peculiar structure of the brain in these young subjects seems to invite the hopeless sequel of hydrocephalus.

CHAPTER XIII

PLAGUE

By W. J. CALVERT, M.D.

Definition.—Plague is an acute infectious disease, running a rapid, severe course, and often terminating fatally. It is generally characterized by extreme weakness, high fever, buboes, and severe general symptoms, and is frequently accompanied by subcutaneous hemorrhages and pustules.

Etiology.—Plague among Animals.—Widespread infections and migration of rats have frequently been observed just before an epidemic, when rats, dead of plague, may be found. Its origin among rats has not been determined, but it probably arises from infected material recently introduced into a district, or it is propagated by mild cases among them. Fleas deserting the dead rat serve to transfer the disease to other animals and man. Flies contract plague; consequently may infect food. They become infected by sucking infected blood, and may transfer bacilli from place to place; their bite produces direct infection. Bacilli may remain virulent in the stomach of bed-bugs for a number of days; their bite during this time may cause infection, and if the insect is mashed on the wound, infection may take place. Ants harbor the bacilli for a number of days, and may carry infection from place to place, especially from cadavers to the surface of the ground.

Climatological Features.—Plague has been observed in frigid and temperate climates, but flourishes best in moderately warm, dry weather, such as is found in the tropics and the subtropics from the end of winter to the rainy season, or usually from January to June. The maximum number of cases usually occurs before the hottest days. In these sections the onset and the close of the epidemic is gradual, with isolated cases throughout the remaining months of the year. This seasonal periodicity is not absolutely constant, yet noticeably frequent. Elevation is of no importance, as the disease flourishes either at the sea level or in very high altitudes.

Portal of Entry.—Owing to the absence of local reaction about the seat of inoculation, it is always difficult and usually impossible to determine this. In inoculation experiments the lymphatic glands draining the inoculated area are most affected. Consequently it is reasonable to infer that a primary bubo indicates in what area the infection occurred. It has been shown that primary buboes occur most frequently in the groin; next, in the axilla. Therefore the majority of infections occur through the skin of the extremities and the trunk. Cases with primary pustule and lymphangitis offer no difficulty, but in others the areas immediately surrounding a scratch or wound are inflamed, making it

impossible to tell through which lesion infection occurred. In children it is thought that infection occurs through abrasions in the buccal mucous membrane. Bacilli introduced into the stomach may or may not produce infection. The probabilities are that infection may enter any abrasion, even a microscopic wound of the skin and mucous membranes.

Direct Transmission.—In every well-advanced case all of the secretions and excretions may contain the organisms in large numbers. Of special importance are the pus from buboes, the excretions from pustules, the vomitus, and the sputum in pneumonic cases. The sputum, sweat, urine, and feces, in given cases, may be infected. Consequently the bedding, furniture, and room may become infected, and those in attendance are continually exposed to direct contact with infected material, and may at any time become infected through abrasions, etc. Notwithstanding this, very few attendants in hospitals have contracted the disease. The cadaver contains many bacilli, and consequently is a dangerous source of infection until disinfected or destroyed. In pneumonic plague, direct transmission is most important, as the sputum is heavily laden with plague bacilli. In the fine droplets of sputum expelled during the act of coughing and in the main masses of sputum the bacilli may be spread broadcast. Direct infection by the deposition of these fine droplets in the faces of attendants may occur.

Indirect Transmission.—The viability of the organism and the relatively small number of bacilli necessary to produce infection are of importance in this connection. The organism is killed by direct sunlight in from two to four hours; protected from sunlight, even under unfavorable conditions, bacilli are capable of retaining life and virulence for an undetermined period. In cultures, full virulence has been noted at fifteen months; on dried paper, at forty-five days; in cadavers, at forty-eight days; and in sputum, at seventy days. Exposures to intense cold does not necessarily kill the organism; 60° C. kills in an hour, and 80° C. in fifteen minutes. To the ordinary disinfectants the bacilli are very susceptible. Considering that even one organism may possibly produce infection, this longevity becomes important, especially in explaining a possible infection of rats and other vermin by old clothing, etc. It has not been shown that air and water carry the organism for any length of time. The long life of the organism and the probable infection through the skin make the hygienic conditions of the highest importance.

Spread of the Disease.—Convalescent patients, especially those with an old unhealed ulcer from a bubo, individuals who have been exposed to infection but have not yet developed the disease, migration of rats and other animals from district to district, and especially on board ship, transportation of clothing and articles of merchandise, especially fabrics and raw materials, are the most important means of carrying the disease from district to district. Flies, fleas, and other insects may carry infection within limited areas.

When introduced into a new district the first few cases are separated by a considerable interval of time, and therefore attract little or no interest, and too often pass undiagnosed. One or two years may

elapse before an epidemic begins. During this time the disease may spread among the rats. After the rats have been infected plague may appear among the inhabitants in isolated cases or in groups—plague centres. The first few cases may establish infected centres from which the disease spreads. These cases do not always occur in the same house or in the same district. The second or third case may be found blocks away from the first known case. After the disease is fairly well established it does not necessarily go from house to house down a given street, but skips about from block to block. Only one member of a large household may suffer from the disease, and months may elapse before a second case occurs in the same house. But after the disease has become well established there are what may be called infected centres or houses in which case after case is found. The usual duration of an epidemic is rarely longer than six months, during which time most of the cases occur within two or three months. Usually the daily number gradually increases to the maximum, followed by a gradual decrease toward the end of the epidemic. The disease is probably kept alive during the interval by mild cases, infected rats and insects, and by infected materials, houses, etc.

Age, Sex, Race, and Occupation.—The young and old of all races are equally susceptible, yet the majority of cases occur between the ages of twenty and forty years, due probably to increased exposure. In childhood and after the age of fifty years the numbers are proportionately small. The apparent immunity of some races living in infected districts is due to good hygienic conditions. Laborers at all trades are affected, but the freedom of workers in oil and water has been noted, probably due to the protection against fleas and the cleansing of the skin by these substances.

Predisposing Factors.—These are fatigue, poor food, insufficient clothing, and the crowding of large numbers into filthy quarters.

Bacteriology.—The *Bacillus pestis bubonicæ*, discovered by Kitasato in 1894, is an encapsulated, non-motile, short, non-spore-forming, aërobic organism, with rounded ends, measuring from 1 to 1.8μ by 0.4 to 0.7μ. As seen in smears from the blood, lymphatic glands, and cultures, it occurs singly, in pairs end to end, and frequently in chains consisting of four to six bacilli; less frequently, especially when grown in liquid media, in very long chains. The capsule varies greatly, apparently influenced by culture media. Ordinarily the capsule of bacilli obtained from the blood or glands is about twice as thick as the organism; in artificial media it is usually not seen. In shape and size the organism varies, depending to some extent on the culture media. Those found in the blood are frequently plumper than those from the lymphatic glands, occasionally resembling cocci. The bacilli take all of the ordinary stains, decolorize in Gram's stain, and very frequently take a bipolar stain, leaving the central portion clear.

Early in the course the bacilli are confined to the infected lymphatic glands or the tissues immediately surrounding them, but as the disease progresses the organisms enter the lymph channels and blood, and are later found in practically every fluid and organ of the body.

Virulence.—The virulence of the plague bacillus varies. A low virulence gives rise to *pestis minor*. These organisms may suddenly become highly virulent, and give rise to the severer forms. The virulence is gradually increased from a low to a high degree by passing the organism through several animals. When high virulence is obtained it is easily maintained in cultures and by passage through animals. Cultures on artificial media retain virulence for months, perhaps years. Mixed infections do not necessarily reduce it. Cold temperatures have practically no effect; higher temperatures, 41° to 42°, reduce virulence.

Toxicity.—When young bouillon cultures are filtered, the filtrate is not highly toxic, showing that the toxins are in combination with the bacterial endotoxin; but when old cultures are filtered, the filtrate is highly toxic, causing widespread hemorrhages, focal areas of necrosis, and fatty degeneration, enlarged spleen, and death; here autolysis has liberated the toxin. When the dose is not fatal, a marasmus may follow with marked loss of weight and hair, anemia, and death after a number of weeks. At autopsy in monkeys the organs seem dry, shrunken, and of a light bronze-green color. Sections show loss of nuclear material and fatty degeneration. When solutions containing toxin are kept over long periods, or are heated, the degree of toxicity diminishes, leaving an immunizing substance undiminished in activity.

Pathology.—The muscles are dark red and dry; about a primary bubo they may be hemorrhagic. The periosteum may be injected or hemorrhagic. The bone-marrow is normal. The synovial membrane of joints near a primary bubo may be hyperemic, rarely hemorrhagic, and the joints may contain a little light straw-colored fluid.

Skin.—The degree of hemorrhage in the skin varies greatly. The hemorrhages are of two types, petechial and diffuse. Petechial hemorrhages occur on the face and upper extremities, but most frequently on the upper part of the trunk. These hemorrhages affect the skin only. The diffuse hemorrhages occur in the subcutaneous tissues and skin, are very large (four or five inches in diameter), irregular in shape, and of a dark bluish-black (often mottled) color. They occur most frequently on the trunk and upper extremities. In both types of hemorrhage bacilli are abundant. About scratches or insect bites a narrow rim of hyperemia or hemorrhage usually occurs. Over large buboes the skin is often hyperemic. Œdema of the skin is rare except over buboes, especially those associated with extensive œdema and in cases with marked nephritis.

Exanthemata resembling wheals frequently occur, often reminding one of mosquito bites. Abscesses may be formed and gangrene sometimes follows a suppurating bubo. Herpes is rarely found, and has not been noted in plague pneumonia. Lymphangitis is rare, occurring both as primary and secondary to pustules and buboes, in which case the skin is thickened, œdematous, and hard, and on section shows bacilli, hemorrhage, hyperemia, and infiltration with leukocytes and small cells.

Primary and Secondary Pustule.—Lodgement of bacilli in the capillaries of the skin may cause an infiltration of the tissues with leukocytes,

small round cells, and red blood cells, œdema, and an extensive invasion of bacilli. These cause an elevation of the epidermis from 2 to 5 or 6 mm., varying in extent from about 0.5 to 2 or 3 cm. in diameter. The edges are sharply raised without an areola. The elevated part is hard, and on section shows œdema, leukocytes, small round cells, red blood cells, and marked congestion. Within a few hours a small vesicle which rapidly enlarges, forms in the centre of the elevated portion, and, in a short time, the bleb covers the entire area. At first the fluid in the bleb is colorless, but soon becomes turbid; then pus forms which often contains blood. This fluid at first usually contains a pure culture of plague bacilli, leukocytes, small round cells, red blood cells, and detritus. The bleb is easily ruptured. When the fluid escapes, a red, swollen, hard base is seen, which soon becomes covered by a grayish or yellowish-gray scab. On section the infiltration extends about 5 mm. into the subcutaneous tissue. The cutis rapidly degenerates until entirely destroyed. All of the bloodvessels of the dermis are greatly dilated, the walls much thinned, and the blood apparently coagulated. In some cases multiple small hemorrhages are noted. The œdema and bacilli from a pustule may extend far beyond its edges into otherwise normal tissue, causing considerable swelling. A red line of œdematous hard tissue may extend from the pustule to the nearest lymphatic gland which is enlarged. Multiple pustules sometimes occur, especially on the body.

Lymphatic System.—The lymphatic glands seem to be the elective seat of development. They may be classed as follows: Glands showing the most pathological changes, usually the first effected, are called *primary buboes;* glands in the chain or glands with the primary bubo, infected by the passage of bacilli through the lymphatic vessels, are called *secondary buboes;* and glands in distant portions of the body, infected through the blood are called *tertiary buboes.* The glands may be grouped as follows: Right and left femoral, including the femoral, inguinal, iliac, and lumbar glands; right and left axillary, including the epitrochlear, axillary, supra- and infraclavicular glands; and the right and left cervical, including the glands about the head, cervical, supra- and infraclavicular.

Primary Bubo.—This is characterized by periglandular œdema, infiltration, and glandular swelling. The œdema is pathognomonic for a primary bubo, and dates from the beginning of the glandular swelling. At this time the areolar tissue between the muscles and tendons about the infected gland is slightly œdematous, of a lemon-yellow color, and soft. As the disease progresses the œdema rapidly extends in all directions, but confines itself entirely to the loose connective tissues. The skin covering the œdematous area is rarely, and the underlying muscles never, affected. In well-developed cases this œdematous tissue looks very much like a soft gelatinous mass, semitranslucent, and of a deep straw or lemon color. On section a thin, clear, straw-colored fluid escapes. This fluid contains a few pus cells, red blood corpuscles, and varying numbers of plague bacilli. The œdema varies from a very slight amount of fluid between the muscles to an amount sufficient to increase the size of the affected region. Œdema associated with a primary

femoral bubo of one side may extend from the knee to the lower portion of the thorax, anteriorly and posteriorly, in the retroperitoneal region as high as the diaphragm and occasionally beyond the median line. The degree of œdema does not depend on the size of the primary bubo. The lymphatic vessels are usually distended, and appear as whitish semitranslucent cords. These œdematous areas resist secondary infections longer than any other portion of the body. Consequently pure cultures of plague bacilli may frequently be obtained here when in all other portions of the body mixed cultures are found.

Periglandular Infiltration.—This, consisting of small round cells and a few leukocytes associated with varying amounts of hemorrhage, is the second characteristic of a primary bubo. It begins in the first hours of glandular enlargement, and rapidly progresses, often extending as much as an inch beyond the capsule of the gland. The infiltrated area is hard, more or less sharply outlined, on section moist, and usually intensely hemorrhagic. The massing of a group of glands into one hard body is caused by periglandular infiltration.

Bubo Proper.—The lymphatic gland begins to enlarge during the first few hours of the disease, progresses rapidly, and usually reaches its maximum size by the fourth day. The primary buboes are from 1 to 4 or 5 cm. in diameter, and vary in shape. Primary buboes during the first five or six days are hard, simulating on palpation a solid rubber ball. During the first twenty-four to forty-eight hours they are isolated and freely movable, but later are firmly fixed by the periglandular infiltration. The capsule is usually greatly distended, often ruptured, and usually shows more or less hemorrhage, making it difficult to differentiate from periglandular infiltration. On section the glandular tissue bulges from pressure; the surface is moist and granular, and in the absence of the hemorrhage the color is grayish, frequently yellowish gray. All degrees of hemorrhage are noted. Frequently the hemorrhages follow the lymph sinuses, producing red columns radiating from the hilus to the periphery of the gland. The centre of the gland is soft but, as a rule, has not advanced to suppuration. After the fifth or sixth day pus may be found. Massive necrosis is caused by the rapid growth of bacilli and the production of toxins. The bacilli evidently lodge in the peripheral lymph sinuses where very large masses of bacteria quickly develop. A few leukocytes, red blood cells, and fragments of tissue may be seen. The lymphatic tissues show all stages of necrosis. The capsule is usually hemorrhagic, and its layers may be widely separated and broken. The periglandular tissue is hemorrhagic, contains varying numbers of leukocytes, and shows a massive small-cell infiltration.

Secondary Buboes.—These differ from the primary buboes in that they lack periglandular œdema, infiltration, and the massive degeneration of the glandular substance, though the œdema arising from the primary bubo may surround them. All the lymph vessels connecting the primary and secondary buboes are greatly distended, appearing as smooth, semitranslucent cords. The tissues immediately surrounding the secondary bubo are usually hemorrhagic. The degree of periglandular hemorrhage varies from a thin layer immediately next the capsule to a

massive hemorrhage extending several inches into the tissues on either side of the gland, often uniting with similar hemorrhages from neighboring glands. The entire retroperitoneal tissue from Poupart's ligament to the diaphragm may present a massive hemorrhage along the chain of iliac and lumbar glands. The bubo is usually hard, freely movable, and, if not hemorrhagic, grayish in color. It may be 3 to 5 cm. in diameter. On section the gland bulges, is usually dry, contains no pus in the centre, and usually presents long, narrow hemorrhagic streaks converging at the hilus, with intermediary grayish or faintly yellowish-gray areas.

Histologically, the secondary buboes are most interesting. From the onset of infection in the primary bubo, toxins, bacilli, and red blood cells pass from it through the lymph vessels into the subcapsular lymph sinuses of the secondary bubo and gradually flow through the sinuses to the hilus of the gland. The red blood cells and bacilli lodge in varying numbers in the sinuses, producing a red hemorrhage-like line through the gland, converging at its hilus. The bacilli continue to grow, forming colonies which in time may overshadow the characteristics of a secondary bubo by reproducing the same conditions as found in a primary bubo. This is rare save in closely located glands.

The toxins at first act as a stimulus on the endothelial cells lining the lymph sinuses. In an early stage it is difficult to decide whether or not multiplication of these cells takes place. No karyokinetic figures have been seen, but the cells seem to be increased in number. A marked increase in the size is noted. Some of the cells are giant in size, and have assumed a phagocytic function. The stimulating stage soon changes to a degenerative one; the nuclear material is gradually lost and takes little or no stain, eventually leaving the nuclei as clear spaces in the protoplasm. Thus far changes have taken place only in and about the edges of the lymph sinus. The centre of the follicle and cords are still unaffected. Gradually the degeneration extends into the lymphatic structure of the follicle, while the centre is yet normal. Degeneration appears about the follicular artery and from this it extends toward the periphery, leaving a horseshoe-shaped band of relatively normal tissue between the degeneration about the lymph sinus and that about the follicular artery. When the follicular artery becomes degenerated, small intrafollicular hemorrhages occur, in the centre of the follicle.

Tertiary Buboes.—These receive infection from the blood, and occur in all portions of the body. The glands are rarely larger than from 1 to 2 cm., freely movable, hard, and hyperemic. On section the tissues are moist and hyperemic. Hemorrhages, which rarely occur until late, are at first intrafollicular and later massive. The first changes occur in the centre of the follicle. A swelling of the endothelial cells lining the trabecular network appears, followed by cessation of lymphocytic production and gradual degeneration of the walls of the capillaries. Phagocytic action of the endothelial cells has not been observed in this region. Hemorrhage about the end of the follicular artery may occur. The outer rim of the follicle and lymph sinus remains intact.

Frequency and Location of Buboes.—Russel records 2641 primary buboes in 2700 cases, or 98.8 per cent.; Wilm, in Hong Kong, 73 per

cent. In the writer's series of 102 autopsies, primary buboes occurred in 101, or 99 per cent.

A *femoral* primary bubo is prominent and hard. The œdema is easily recognized, often extending from the knee to the lower border of the thorax anteriorly. When the œdema is well-developed the bubo may on palpation apparently fluctuate, but on section is usually hard. The closely located inguinal glands may escape infection, none of them being more than slightly enlarged; one gland in the group may be very large, or the entire group may become affected and united by the periglandular infiltration into one solid mass. On section this mass has a very characteristic picture. The cut surface presents a deep red, congested, or intensely hemorrhagic tissue, dotted here and there with sections of the numerous lymphatic glands, which have a grayish or yellowish-gray color mixed with hemorrhagic areas not so deep in color as the red of the infiltrated periglandular tissue. Add to this the extensive œdema and one has a pathognomonic picture. The iliac glands may escape infection; only one, or all, may become enlarged, hardened, and surrounded by hemorrhagic tissue or a massive hemorrhage throughout the retroperitoneal tissue may occur. In the lumbar and pelvic glands the same condition may exist. Often, owing to a backward flow of lymph, the iliac and inguinal glands of the opposite side may show secondary buboes. Owing to the proximity of the inguinal glands to the primary femoral bubo they may rapidly assume all its characteristics. Other glands involved are tertiary buboes. Primary inguinal, axillary, and cervical buboes present pictures similar to that described for the femoral bubo, modified only by anatomical position.

Development and Fate of Buboes.—No set order of development of a primary bubo exists. Generally speaking, three groups may be noted, as follows: (1) Early development of primary buboes. When the first general symptoms of the disease are noted, one gland is more prominent than the remaining glands of the group. Often this gland has not been noticed by the patient; in others the initial pain is severe. (2) The primary bubo begins to develop a few hours after the general symptoms. (3) Twenty-four to forty-eight hours elapse before the glands begin to enlarge. After a gland begins to enlarge its progress is usually very rapid, reaching its maximum in from four to six days. Suppuration takes place during the second week, about the tenth day, and is caused by secondary infection. In a majority of fatal cases death occurs before suppuration takes place. In the event of recovery the primary buboes may not suppurate, resolution taking place; or suppuration may occur, often giving rise to gangrene which, on account of lowered resistance, is severe and requires weeks, often months, to heal, or which may be the immediate cause of death. The outcome of suppurating buboes is similar to other infections, but usually requires a much longer time for healing. Secondary buboes begin to develop within a few hours after the onset of the primary bubo. When the primary bubo is one of a group, as an inguinal, it is often difficult to determine which is the primary and which the secondary bubo. Suppuration rarely occurs. During convalescence the glands return to normal size. Tertiary buboes

appear quite early, following the entrance of toxins into the system. On account of the frequent occurrence of slightly enlarged glands it is difficult to determine when the enlargement first begins. Suppuration rarely occurs.

Respiratory System.—The nasal mucous membrane is negative. The pharynx, larynx, and trachea are frequently hyperemic, often having an intense dark violet-blue color, sometimes hemorrhagic. In the last stage of the disease œdema of the glottis may be present. Congestion and œdema of the lungs are common, and varying degrees of bronchitis and bronchopneumonia occur. The pleura, both viscera and parietal, frequently show punctate hemorrhages and often hydrops, especially late in the course. The lymphatic glands at the base of the lung and in the mediastinum are enlarged, with the characters of tertiary buboes.

Pneumonia.—The consolidation may be extensive, but is more frequently lobular. By the union of a number of lobules small consolidated areas are formed, which on section are red and hard. The lobule is filled with red blood cells, masses of bacteria, and but little serum. The alveolar walls are thickened and the vessels congested. Blood and masses of bacilli are found in the bronchi.

Circulatory System.—*Pericardium.*—The pericardial sac may contain a few centimeters of light straw-colored fluid. In the parietal layer the vessels are congested, and on the outer and inner surface numerous punctate or diffuse hemorrhages may be noted. On the visceral layer subpericardial hemorrhages, punctate or diffuse, are more common.

Heart.—The right heart is, as a rule, much distended, the left heart empty, the vessels distended, and the muscle flabby, showing parenchymatous and fatty degeneration. Often the intramuscular vessels are distended with leukocytes, and intramuscular hemorrhages occur. The heart valves and endocardium are normal save an occasional subendocardial hemorrhage. Very few lesions are to be found in the arteries. Periglandular infiltration may extend through the walls of a neighboring bloodvessel, causing massive hemorrhage and infiltration of the vessel walls, sometimes associated with a thrombus. Inflammation along a vas vasorum is sometimes noted. The capillaries are usually much distended, sometimes thrombosed, often ruptured, causing extensive hemorrhages. Extreme congestion of the general venous system is one of the most striking conditions at autopsy.

Spleen.—This is frequently enlarged, varying from normal to three or four times the original size. A typical plague spleen is firm, the capsule tense with perhaps a few subcapsular hemorrhages, and reddish brown. On section the tissue bulges, the surface is dry or very slightly moist, the color red with a bluish-purple cast; the Malpighian corpuscles and trabeculæ are visible with frequent hemorrhages; the pulp is increased. The tissues are widely separated, with the small round cells and polymorphonuclear leukocytes increased, and some desquamation of endothelial cells lining the membranes. The fixed elements show varying degrees of cloudy swelling and fatty degeneration. Focal areas of necrosis are sometimes observed. Plague bacilli are seen in masses, scattered through the tissues, and intracellular.

Digestive Tract.—The mucous membrane of the mouth is usually dry; more or less hyperemic, occasionally hemorrhagic, and frequently covered with a whitish or yellowish-white coat. The tongue is usually coated white; later, especially along the median line, the coat turns brown to brownish black. The edges of the tongue are clean, red, and œdematous. The papillæ are prominent. The tonsils may be enlarged, hyperemic, coated white, or yellowish white; occasionally they show considerable enlargement, followed by pus formation and necrosis. In ordinary cases the sputum is negative, but when the disease has become systemic, and in pneumonic cases, it may contain bacilli. The œsophagus is rarely affected, save by an occasional punctate hemorrhage. In the stomach no constant lesions are found. The mucous membrane is often hyperemic and studded with punctate hemorrhage. Frequently there is an acute catarrhal gastritis with hypersecretion and more or less altered blood. The lymphatic structures may be swollen. The mucous membrane of the intestines may be hyperemic, and hemorrhagic especially in the duodenum. The solitary follicles and Peyer's patches are swollen, but rarely show degenerative changes. Occasionally ulceration takes place. The mesenteric glands are usually enlarged and hyperemic, but rarely hemorrhagic. About the cecum a chain of glands is frequently large enough to palpate. The peritoneum is usually dry. Peritonitis sometimes occurs over an enlarged iliac gland. In the cases observed there was a thick, yellowish-gray, cheesy layer over the affected peritoneum.

Liver.—This is slightly enlarged and congested. Its surface presents more or less subcapsular hemorrhage, especially about the suspensory ligament, together with areas of fatty degeneration varying in size, and of a soft yellowish-white color. The lobules may be of a light color with the central vein prominent. A section shows cloudy swelling, areas of fatty degeneration, and distension of bloodvessels. Hemorrhages rarely occur in the substance of the liver. Stained sections show varying degrees of parenchymatous degeneration and usually considerable fatty degeneration, which in areas completely obliterates the protoplasm of the cells and is most marked in the periphery of the lobule and in the area nearest the arterial blood supply. Focal areas of degeneration are found, containing broken-down cells, bacilli, and more or less blood.

Pancreas.—This presents no changes save a large or small number of punctate hemorrhages.

Genito-urinary System.—The adrenals present no changes. The kidneys may show no changes; but varying amounts of subcapsular and punctate hemorrhages may be found, with varying degrees of parenchymatous and fatty degeneration. The organ is frequently congested. The pelvis is particularly prone to hemorrhage, either punctate or general. In the ureters and bladder hemorrhages sometimes occur. Cystitis is rare. Severe uterine hemorrhage, especially at a period, is common, and abortion usually occurs in the pregnant. Œdema of the labia is not uncommon.

Urine.—The urine is usually diminished in quantity, of a high color, and of high specific gravity; contains a small amount of albumin, globulin,

indican, and diminished chlorides, but no sugar. Epithelial cells, varying amounts of pus, and red blood cells, with many granular and fatty casts, are found. The blood in the urine depends more on the amount of hemorrhage along the urinary tract than on the degree of acute nephritis. Suppression of urine is common, especially in the later stages. Plague bacilli occur in the urine. One case of urethral discharge was found to consist entirely of semen containing numerous pus cells with a pure culture of plague bacilli.

Nervous System.—Anatomical changes are rare. There are varying degrees of hyperemia, with an occasional punctate hemorrhage in the meninges. Meningitis occasionally occurs. The nervous manifestations are largely functional, due to toxemia and congestion.

Special Senses.—Rarely affections of the ear arise from extension of inflammation, from primary cervical buboes, and from hemorrhage. Conjunctivitis is common, and keratitis, iridocyclitis, and hypopyon occur, sometimes going on to panophthalmitis.

Inoculation Experiments.—Practically all animals are susceptible to plague. Subcutaneous inoculation of a fatal dose produces a swelling about the seat of inoculation which, on section, shows marked œdema, varying degrees of hemorrhage, usually extensive, and infiltration of small round cells, few leukocytes, and varying numbers of red blood cells. The nearest lymphatic glands are enlarged, hyperemic or hemorrhagic, and hard; on section they show the changes found in the secondary bubo. Rarely is a primary bubo found, but if the clinical course is long, one may develop and go on to suppuration. Rats have been observed with large ulcers, probably the result of plague buboes. All of the lymphatic glands are enlarged, hard, and hyperemic; on section, the changes incidental to tertiary buboes are present. The blood shows a leukocytosis and plague bacilli varying according to the duration of the infection, but usually in large numbers. There is a remarkable similarity to the lesions found in human cadavers.

Symptoms.—Incubation Period.—From observations in isolation camps and accidental infections this has been found to vary from two to ten days. A few authors give fifteen days as the longest period.

The clinical manifestations are very varied. The most important varieties are pestis minor, abortive or ambulatory plague, pestis bubonicæ, or bubonic plague, septicemic plague, pneumonic and intestinal plague.

General Symptomatology.—The main features are a sudden onset, rapid development of severe symptoms such as high fever, severe prostration (often reaching a typhoid state within forty-eight hours), severe vomiting (often bloody), intense pain, headache, and pain about the buboes; severe nervous symptoms, such as restlessness, sleeplessness, delirium, epileptiform seizures, and coma followed by death within two to four days. The prostration is out of all proportion to the degree of fever and duration of the disease; there is a most peculiar facial expression, with the eyes bright and staring as if looking at a distant object; the conjunctivæ are injected and the nostrils dilated; the face expresses pain, fear, and anxiety; the respiration is hurried and labored; the body is flexed. This picture, when once seen, cannot be forgotten.

Fever.—There is no characteristic fever-curve. Generally the symptoms are out of proportion to the degree of fever, which rarely exceeds 104° F.; it occasionally reaches 107° F. The onset is not constant. In the first days a gradual rise is noted, reaching a maximum on the third or fourth day; after this time a gradual decline occurs. More often the onset is with a sudden rise as high as 103° or 104° F., after which there is in some cases continuous fever with daily remission and afternoon or evening rise. Frequently a remittent type occurs with morning remissions of from 1.5° to 2°. Occasionally a true remittent type is present, the temperature falling to 96° or 97° F. A continuous curve for from two to three days may be followed by a drop of from 2° to 3° or even to a subnormal temperature, to be followed by a rise above the highest temperature yet noted. In the second rise a remittent curve is usually present. Marked irregularity is perhaps the most constant feature. Sudden drops to normal or subnormal are not rare, and variations of from 2° to 3° are very common. Just before death there may be a drop of 3° or 4° to or below normal, followed by a sudden rise of 4° to 5°, and death. The fever continues from six days to four or five weeks, usually from six to ten days, and subsides, as a rule, by lysis to normal, or frequently to a subnormal temperature which may last several days. After several days of normal or subnormal temperature a second rise may occur. With suppuration the temperature is of the septic type, which rapidly subsides after drainage. In some cases even with marked buboes and general symptoms, only a degree or two of fever may be noted. As a rule the cases with very high temperature are fatal; yet the degree of fever is not good prognostic evidence.

Pulse.—In no other infectious disease does the heart weakness manifest itself so early and so severely. Frequently at the end of the first, rarely later than the third day, pronounced symptoms of heart weakness are present. The pulse during the first few days is full, large, of moderate tension, and often dicrotic; later it is small, weak, equal, regular, or often intermittent. The development of septicemia has no influence on the pulse. The rate varies from about 120 to 180, and frequently late in the disease is much higher. Pulsus paradoxus has been noted. In very severe cases the pulse may become so weak and rapid that it is impossible to count it at the wrist. During convalescence a rapid, weak, and often intermittent pulse is present for an indefinite time.

Blood.—No change in the red blood cells is noted, although a slight diminution in their number and hemoglobin content has been mentioned. A polymorphonuclear leukocytosis begins with the disease, varying from 8000 to 45,000 per cmm. The blood platelets are usually greatly increased. Plague bacilli enter the blood through the lymphatic vessels and by direct growth into a vessel through the tissues about a primary bubo. There is a progressive septicemia, beginning a few hours after the onset and increasing until just before death, when the blood practically becomes a pure culture of bacilli. Clumps of bacilli are often observed in the peripheral circulation, and many, being too large to pass the capillaries, form emboli and new colonies of bacilli, which

grow through the walls of the vessel into the tissues, causing hemorrhage and frequently leading to thrombosis and pustules.

Duration.—Plague runs a most varied course. Fatal cases last from eighteen hours to fifteen days, but the majority terminate before the sixth day. Septicemic plague is fatal in from eighteen hours to seven or eight days, usually before the fifth day. The pneumonic type is fatal in from two to seven or eight days, usually before the fifth. The bubonic type in the majority of cases is fatal before the sixth day. Generally speaking, if the patient lives through the fifth day his chances for recovery are good. Convalescence is often complicated by successive suppuration of a number of lymphatic glands, and by severe heart weakness, often protracted for months.

Pestis Minor, Abortive, or Ambulatory Plague.—Pestis minor occurs during several months or a year previous to a general epidemic. The symptoms are light and very varied. One or more lymphatic glands, the inguinal most frequently, are swollen, more or less painful, and usually go on to resolution, but rarely to suppuration. Few bacilli are found in the blood, while relatively large numbers are present in the fluid from a bubo. These organisms are not highly pathogenic. The general symptoms are slight headache, general malaise, occasional vomiting, heart palpitation, slight diarrhœa or constipation, and low fever. The picture varies from simply an enlarged lymphatic gland to one with all the above symptoms in moderate degree. After a severe epidemic many cases of pestis minor occur, especially in infected centres. Some observers think that many so-called cases of pestis minor are climatic buboes. These must be differentiated from venereal buboes, dengue, and any of the infectious diseases with enlarged lymphatic glands.

Bubonic Plague.—The prodromal symptoms are general malaise, weakness, slight chills, pains in the head and limbs, sleeplessness, loss of appetite, vomiting, palpitation, and aching in the region of the future primary bubo. The onset is often accompanied by high fever, which may reach its height the first day, but more commonly, not until the second or third day, and is usually associated with slight initial chills. It is not uncommon for the chills to continue at short intervals throughout the course. The fever may rise gradually, reaching its maximum about the fourth or fifth day. As a rule it is very irregular, frequently being intermittent and usually showing a daily remission of from 1° to 2°. In the usual favorable case fever lasts from seven or eight to ten days, when, as a rule, it subsides by lysis to, or a little below, normal for a number of days. After several days there may be, even in uncomplicated cases, a rise of 1° or more for a short period. If suppuration occurs during the second week, a septic fever-curve may be present until the abscess is drained. In fatal cases the temperature may drop from 103° or 104° F. to or below normal within a few minutes, followed by a rapid rise to or above the previous temperature, and death; or the temperature may rise from 103° or 104° to 105° or even 107° F., to be followed by death. A dull aching pain in the region of the primary bubo sometimes precedes all other symptoms, but more often fever develops first. As the buboes develop rapidly, pain due to the stretching

of the tissues is severe, limited mostly to the region of the bubo. Pain continues until the active process has subsided; then the patient is fairly comfortable until suppuration begins, during the second week. It is more frequent than resolution. On account of the pain the patient assumes the position best suited to relieve pressure on the affected glands—that is, flexion of the leg on the trunk in primary inguinal bubo, the arm close to the trunk in primary axillary bubo, and the head to the affected side in primary cervical bubo. Internal glands may or may not be painful, but if large and numerous, severe pain is common. It is especially noted on pressure along the inguinal chain, and when the mesenteric glands are large, general pain over the abdomen is often severe. Suppuration of internal glands may lead to severe complications. The conjunctivæ are reddened, the pupils equal, often dilated, or more rarely contracted. In advanced cases the eyes are sunken and lusterless, with the corona somewhat clouded. In others the eyes are bright, staring, and may have an intense, anxious expression. The nostrils are widely dilated and move with each inspiration.

The mucous membranes may be normal or somewhat hyperemic. The tongue is slightly swollen, covered with a white coat, with prominent papillæ, the edges clean, bright red, and showing the imprint of the teeth. Later, especially in the centre, the coat turns to a dirty blackish-brown color. The buccal mucous membrane is red, œdematous, and occasionally covered with a whitish coat. The pharynx is red, often bluish from congestion, and occasionally coated. The tonsils may be swollen and hyperemic. Later in the disease the skin may show, over the face, trunk, and upper extremities, numerous small, punctate bright red hemorrhages or, less seldom, over the trunk and upper extremities, diffuse, large, irregular, subcutaneous hemorrhages of a bluish-black color. During the first days the skin is dry and hot; later periodical or continuous profuse sweating may occur. Some authors ascribe a peculiar odor to plague patients. The pulse is rapid, small, of low tension, often dicrotic, and rarely less than 100 and often 180. The respirations are rapid (40 to 60 per minute), superficial and labored. At this time the patient, with his anxious expression, quickened respiration, and flexed attitude, presents a pathognomonic picture which once seen suffices for a ready diagnosis. The heart is usually somewhat dilated, and may have soft systolic murmurs at the base. The lungs may show harsh breath sounds, and a few rales, probably due to congestion and œdema. The spleen is often enlarged, but rarely reaches more than about 1 cm. below the costal margin. The liver may often be felt. Diarrhœa or constipation may be present or alternate. The abdomen, unless the deep or mesenteric lymphatic glands are enlarged, is negative. The urine is diminished in quantity and occasionally retention may occur, more rarely anuria, especially for a few hours before death. The nervous symptoms are varied. Vomiting is common at the onset and through the first few days. Headache may be severe and at the onset the degree of prostration may be phenomenal, the patient reaching a typhoid state within two or three days. Again, the patient is restless, tossing about, excited even to delirium, talkative or

crying by turns, even crazed, leaving the bed only to pass into epileptic seizures and fall on the floor, there to remain unconscious for a longer or shorter time. Awakening from this state, he may suffer intense pain, often relieved by passing into a benumbed or unconscious state. For a few hours before death coma is not uncommon. In other cases consciousness may be retained until the last. Owing probably to congestion, symptoms suggestive of meningitis may be present.

Septicemic or Fulminating Plague.—The onset is sudden, with high fever, prostration, and delirium. Prodromal symptoms may or may not be present. All of the symptoms are rapid and severe. All of the lymphatic glands are more or less enlarged and painful, but no primary bubo develops. The prostration is severe from the beginning and coma may develop early. Vomiting is often persistent and severe. Bloody diarrhœa is frequent. The pulse is rapid and of low tension. The spleen rapidly enlarges and is easily palpated. Death almost invariably results in from eighteen hours to three days after the onset. These cases are often intensely hemorrhagic.

Pneumonic Plague.[1]—Pneumonia occurs in two forms: (1) Lobar pneumonia caused by the pneumococcus, and (2) true plague pneumonia. Plague pneumonia is either primary or secondary. In primary plague pneumonia prodromal symptoms are rare. The onset is usually sudden, with a rapid rise of fever, frequently accompanied by a severe chill or chills, and rapidly followed by intense headache, general body pains, vomiting, and severe prostration. The fever is high and usually irregular, occasionally intermittent; the pulse weak, of low tension, and rapid. The heart is weak and, owing to a compensating emphysema, may present a diminished area of dulness. Again, owing to dilatation of the heart, increased dulness especially to the right side may be noted. The spleen is enlarged in the majority of cases. The respiration is rapid, reaching 75 or over per minute. Cyanosis is usually marked. Septicemia develops early. The general symptoms described for bubonic plague, excepting buboes, may be noted in pneumonic plague.

Plague pneumonia occurs in two forms, the bronchitic with limited bronchopneumonia, and a more extensive consolidation, lobar, with bronchitis. In both types cough is present. The bronchitic form presents a serous frothy sputum with more or less blood and often a pure culture of plague bacilli. The physical signs are normal vocal fremitus, possibly slight dulness, harsh breath sounds, and fine crepitant rales. As the consolidated areas increase, the sputum contains more blood and the dulness is more extensive. Often small, dull areas may be outlined. In the more consolidated type vocal fremitus is increased; the breath sounds are rough and more tubular; crepitant, moist, and piping rales are common; and the consolidated areas are larger, perhaps involving an entire lobe. The sputum is almost pure blood, bright red and frothy, but is rarely tenacious. Dyspnœa and cyanosis are extreme. The intensely bloody sputum rarely occurs before the second or third

[1] For a full discussion, including methods of spreading of plague, prophylaxis, etc., consult *International Plague Conference*, Mukden, 1911, Manila, 1912, Bur. Print.

day. Vomitus rich in blood, and bloody diarrhœa are common. Pleural friction with pain is early and severe. Occasionally fluid collects in the pleural sac. The nervous manifestations are similar to bubonic plague. The duration of the disease varies from two to eight days, but usually death occurs within five days. Diagnosis is difficult and, in the bronchitic type, may be overlooked until autopsy. The glands at the base of the lungs are enlarged and surrounded by œdema. Other glands may enlarge, as in the bubonic type.

Secondary pneumonia develops from emboli or aspiration of infected material. Emboli arise from clumps of bacilli often found in the peripheral circulation, and from dislodgement of a portion or all of the small thrombus which commonly forms in the capillaries. Mural thrombi in the veins near a primary bubo may give rise to emboli. Clinically the two forms cannot be differentiated and frequently are entirely overlooked. The embolic pneumonia may occur early in the course, the aspiration form usually toward the end, and regular lobar pneumonia in the last part of the course. The embolic type usually shows numerous areas of consolidation throughout the lung, while the aspiration form is more often limited to the lower lobes. Clinically the increased respiration and cyanosis are of no diagnostic value, as both occur in non-pneumonic cases. Rales and small areas of dulness may lead to a diagnosis, especially if near the surface. A pleural friction rub is common.

Intestinal Plague.—In this form the lymphatics of the intestines and mesenteric glands are most affected. The onset and general symptoms are as previously described, save for the presence of marked vomiting of bloody material, bloody diarrhœa, and intense pains throughout the abdomen. Buboes are absent.

Sequelæ.—Various nervous affections, such as paralyses of various kinds, may follow plague. Inflammation may appear in the joints, middle ear, and especially in buboes, one after another. Protracted heart weakness may continue for an indefinite period. Gangrene of the lung and protracted hemorrhage from the urinary passages are not uncommon. Suppuration of internal buboes may lead to abscess formation in the peritoneal cavity or mediastinum.

Diagnosis.—During an epidemic this is very easy, especially the bubonic type; but before and after an epidemic, and especially before the presence of plague is known or suspected, a diagnosis is difficult. The first cases may present only a small swelling of a lymphatic gland with or without light general symptoms. Here the presence of plague bacilli in these glands and frequently in the blood is of great importance, and no time should be lost in puncturing the bubo with a hypodermic needle, and in extracting fluid with which to inoculate a mouse, rat, or guinea-pig, and for the purpose of making cultures. The results will give a positive diagnosis within a few days.

Climatic Buboes.—Light attacks with buboes and slight general symptoms must be differentiated from the climatic buboes which usually occur in the groin, are painful, and may go on to suppuration with fever. Their course is about one week. They occur sporadically or in light epidemic form. Bacteriologically the buboes and blood are negative.

Febrile Adenitis.—This occurs usually in children, sporadically or in epidemic forms. The glands of the neck, occasionally of the axillæ, are enlarged and painful. Fever may reach 103° to 104° F., but generally the disease is light and lasts but a few days. The glands and blood are negative bacteriologically.

Venereal Buboes.—Venereal buboes may simulate a light attack of plague. Here the history and bacteriological findings serve to differentiate.

Infectious Diseases.—Most of the infectious diseases may cause enlargement of the lymphatic glands. Here the clinical picture, the severity of the attack, and the bacteriological examination distinguish the disease. Plague without buboes may simulate malaria, typhoid, and relapsing fever. Here the history is of importance, but careful bacteriological examination should suffice within a few hours. In the tropics and the subtropics dengue fever with enlarged lymphatic glands must be considered. In such cases the subsequent clinical picture, pain about the points and muscles, the rash, and negative bacteriological findings are distinctive. Diphtheria with minor throat symptoms is easily differentiated. In cases with severe involvement of the mesenteric glands, especially those about the cecum, and with a large tender iliac gland, appendicitis is suggested. Here a blood examination may be of value. An increase of blood-platelets may suggest plague. The development of a bubo would determine the diagnosis. Isolated cases of plague pneumonia may go unnoticed. Here the sputum, rapid respiration, cyanosis, severe prostration, and enlarged spleen should suggest a bacteriological examination. Skin lesions present no difficulty. A primary pustule may be differentiated from a malignant pustule by the bacteriological finding. In the absence of an epidemic a microscopic and bacteriological examination is the only possible means to a sure diagnosis. Even then some experience is often necessary. Fatal cases should go to autopsy, when the general venous engorgement, hemorrhagic character of all the organs, fatty liver, large, hard spleen, enlarged lymphatic glands, and the presence of a bipolar bacillus suffice for a tentative diagnosis until the organism has been identified.

Serum Diagnosis.—Agglutination of plague bacilli by serum from plague patients rarely occurs during the first week, more often in the second, and quite constantly in the third and fourth weeks; so that agglutination is of no value until late in convalescence.

Prognosis.—This depends on the general severity of the existing epidemic. The death-rate varies from 30 to 99 per cent. The general condition of the patient and the type of plague are the most important factors. In order of severity the types are pneumonic, septicemic, bubonic, and pestis minor. Prognostication is of little value during the course except in pestis minor. Clinically, the degree of dilatation of the heart and the strength of its beat are perhaps most trustworthy.

Prophylaxis.—When plague is suspected an early diagnosis is all-important. Thereafter the disease should be handled in a general and special way. An efficient corps should be organized for the purpose of cleaning every nook and corner of the city or district where the case

appears, and for reporting every case of sickness, which should be visited at once. Every plague patient should be removed to an isolated plague hospital, and the inmates of the house should be placed in quarantine. General detention quarantine camps are questionable, for here many may be exposed for the first time to infection. Information should be given of the nature of plague and the town should be placarded with warnings regarding protection of the feet and legs; cleanliness of the house, clothing, person, and food; disposition of garbage, infected material, etc.

Rats[1] are perhaps the most important means of spreading plague. The rat contracts the disease, enters the house, and dies; then the harbored fleas leave the dead rat to feed on man. The infected flea either introduces the bacilli into the wound caused by the bite or upon the skin. In the later event the bacilli are rubbed into small wounds by the clothing. Consequently the destruction of rats and the rat-proofing of all structures, especially docks and warehouses, are most important. The hearty coöperation of the public with the officials in charge of the plague work should be enlisted. At the plague hospital and detention camp should be men skilled in the diagnosis of plague, to diminish as far as possible further exposure to infection. Infected houses or centres, clothing, furniture, etc., should be destroyed at the public expense. All articles capable of disinfection without injury should be disinfected. The general disinfection of the houses and their contents and the destruction of rats, mice, insects, etc., should be done as rapidly as possible. An early removal, followed by disinfection—better, destruction—of the dead is desirable.

In pneumonic plague extreme care is necessary. Here the bacilli are discharged in the sputum. Especially constructed beds and hospitals are recommended. The isolation of all cases and contacts is important on account of direct transmission. The regulation of sleeping quarters is necessary; overcrowding should be prohibited.

Quarantine, to be of value, must be rigorous. Convalescents, infected materials (particularly fabrics), and rats (especially on board vessels) may carry infection. Effective quarantine measures would curtail commercial movements to what might be considered by business men an unwarrantable degree. Nevertheless, districts free from plague should insist on an absolute quarantine, since plague once introduced into a community is almost impossible of eradication.

Prophylactic Inoculation.—Various preparations have been used to produce a protective immunity. Agar cultures recovered in salt solution and killed, old killed bouillon cultures, Lustig's neucleoprotein, and attenuated living cultures have been used. All of these preparations produce a well-defined reaction, which is followed by a certain amount of immunity. This, according to statistics, is of undoubted value against the bubonic form, but is apparently of almost no value against the

[1] Chick and Martin (*Journal of Hygiene*, March, 1911) give the geographical distribution of fleas. Abstracts of the important literature on plague, fleas, rats, etc., are given in *Second Review in Recent Advances in Tropical Medicine*, by Balfour and Archibald.

pneumonic type. Observations on the value of these preparations warrant the hope that a protective immunity may be developed.

The immunity conferred by the intravenous and subcutaneous injections of large amounts of antitoxin is very temporary, lasting only a limited number of days, in the opinion of some, not longer than five days. Consequently such passive immunity is not at this time of much service as a prophylactic.

Treatment.—Symptomatic treatment is indicated. An initial purgative is good. Stimulants should be used, and, if fever is high, cold applications are of value. Some use is made of antipyretic drugs. Bichloride of mercury in large doses is recommended. For the headache, an ice-cap is preferable to drugs. For vomiting, cold applications to the epigastrium and ordinary remedies may be used. In severe hemorrhagic cases styptics are indicated. In violent or very restless cases hyoscine is of service. No treatment for the buboes will be effective until fluctuation suggests surgical intervention. Excision of buboes is of doubtful service, and is often followed by serious results. In convalescence stimulants are valuable. All skin lesions should receive antiseptic treatment. Antitoxin, when used in large quantities, intravenously and subcutaneously, and early in the course of the disease, serves to prolong the duration and in some instances is undoubtedly responsible for recovery. As yet an antitoxin of the desired strength has not been obtained.

CHAPTER XIV

ANTHRAX AND GLANDERS

By MAZŸCK P. RAVENEL, M.D.

ANTHRAX

Synonyms.—English, Splenic Fever, Woolsorters' Disease, Malignant Pustule, Anthracemia; French, Charbon, Sang-de-rate, Mal-de-rate, Fièvre Charbonneuse, Charbon Bactéridien, Anthrax; German, Milzbrand.

Definition.—Anthrax is a specific and highly contagious disease common to man and most domestic animals, due to the *Bacillus anthracis*. It occurs in two principal forms: an external, due to direct inoculation through a cut or abrasion, and an internal, caused by ingestion or inhalation of the spores or bacilli.

Anthrax in Animals.—Since anthrax in man is always derived from animals either directly or indirectly, its distribution is a matter of importance. It is found in practically every part of the world, but is especially prevalent in parts of France, Germany, Austria, Italy, Turkey, Russia, China, South Africa, and South America. Considerable losses occur in the United States from time to time, in widely separated parts of the country. In countries where it is endemic it is especially active during certain years. The herbivorous animals are particularly affected. In Russia, large numbers of horses perish from the disease, and their hair, which is largely used in manufactures, is responsible for the infection of man in distant portions of the world. The most dangerous hair comes from China, Russia, and Siberia. In Asia Minor, anthrax is prevalent among the Angora goats, which supply much of the mohair of commerce.

Anthrax does not spread from animal to animal by contact or association, infection taking place, as a rule, through the intestine, from the ingestion of forage containing the spores. The refuse from tanneries and the washings from infected wools have been proved to play an important part in the spread of anthrax, through the infection of pastures. A striking instance of infection from tanneries occurred in Pennsylvania, where, almost simultaneously, anthrax appeared among the operatives of three tanneries quite widely separated, and in the cattle pastured on the streams which received their drainage. The source of infection proved to be a cargo of hides from China which had been divided among the three plants. In Delaware, the morocco works using goat skins from South America are a frequent source of infection for native cattle. Houston found anthrax bacilli in the mud of the river Yeo in England.

The dust from factories working up infected materials may also spread the disease, as in the case reported by Silberschmidt at Zurich, where 8

out of 22 horses were infected by grazing in a lot exposed to the dust from a horse-hair factory.

A field once infected is difficult to rid of anthrax. Pasteur showed that the spores from soil infected by the blood and corpses of animals which had died of anthrax were brought to the surface by earth-worms. Fields are also infected by the use of waste products from tanneries and factories as fertilizer.

In lessening the ravages of anthrax, Pasteur's method of vaccination has played an important part, and should be practised in horses, sheep, cattle, etc., whenever exposed. Unfortunately the immunity produced is not lasting, but usually one vaccination a year is found sufficient. Infected premises must be cleansed and disinfected, and cattle from infected herds should not be carried into new districts. Most important is the destruction of the carcasses of dead animals. Whenever possible they should be burned. Failing this, they must be deeply buried and covered with quick-lime. Under no circumstances should the skin be removed or the body opened, as this admits oxygen and allows the formation of spores. In the absence of spores the anthrax bacillus is rapidly destroyed during putrefaction.

Etiology.—Anthrax in man is always derived from some domestic animal, or from some commercial animal product, especially the hide, hair, or wool. The bacillus does not penetrate the unbroken skin, but enters some abrasion, scratch, or cut.

In the United States it occurs almost exclusively among veterinarians, brush-makers, leather-workers, and tanners. Farmers are sometimes inoculated while skinning animals which have died of anthrax, and butchers from handling the meat of diseased cattle. Among others who are especially exposed to contagion are knackers, plasterers, felt-makers, and mattress-makers. Human anthrax is especially frequent in Italy, from which country 36,426 cases have been reported in fifteen years. Internal anthrax is almost unknown in this country. It is quite common in certain portions of England, notably the Bradford district, where wool and hair from many parts of the world are manufactured, and which receives almost the total importation of what are known as dangerous wools. Much of our knowledge of this type of the disease has come from the studies made in this district, where it has received the name "woolsorters' disease."

It was first observed after the introduction of alpaca and mohair, in 1837. Outbreaks occurred from time to time but the etiology was not definitely demonstrated until 1880, when Mr. Spear and Professor Greenfield made an exhaustive investigation at the instance of the Local Government Board, although in 1879, Bell had successfully inoculated animals with the blood of an alpaca sorter shortly before death, and recovered anthrax bacilli from their blood, being the first to recognize the disease as anthrax.

Infection takes place usually in the sorting, combing, and spinning of the wool, and is due to the inhalation of the spores of anthrax which are given off in the dust arising from the wool of diseased animals during these operations. Other things being equal, the danger from wool

and hair is inversely proportioned to their moisture or greasiness, which prevent the spore-containing dust from flying off. Cutaneous inoculation takes place from greasy wools, but never the internal form. The hair of goats, cows, horses, alpacas, etc., does not contain any greasy matter, and is especially dangerous. Even where goats and sheep are herded together and thus exposed in the same degree to anthrax, the wool will be comparatively safe to work with, while the hair from goats equally contaminated will be dangerous. Blood-stained fleeces are particularly apt to harbor anthrax spores. Among 139 blood-stained samples examined by Dr. Eurich, 14.4 per cent. were found to carry anthrax germs, often in great numbers, while approximately 600 unstained samples gave entirely negative results.

The comparative danger from various materials is illustrated by English statistics for 1899 to 1907 inclusive, during which time 447 cases of all forms of anthrax were reported with 120 deaths, as follows:

Workers in worsted and wool	175 cases, 47 deaths	= 26.8% mortality
Workers in horse-hair and bristles . .	104 cases, 26 deaths	= 25.4% mortality
Workers in hides and skins	131 cases, 34 deaths	= 26.6% mortality
Workers in other industries	37 cases, 13 deaths	= 37.0% mortality

Workers in hides and skins acquire almost exclusively external anthrax. In London, of 92 cases observed among those working in the hide and skin trades, only 2 were intestinal, while of 87 cases in the Bradford worsted districts, 30 were external and 57 internal in form. The very fatal disease (*Hadernkrankheit*) in rag-pickers in the paper mills in lower Austria has been shown by Frisch and Eppinger to be internal anthrax.

Gastro-intestinal anthrax may result from eating the flesh or drinking the milk of animals with the disease. Fortunately, the disease is so rapid in its course that danger from these sources is not very great. The writer has known an animal in the last stages of anthrax to be slaughtered and dressed for market by a thrifty farmer who saw his cow about to die, and wished to avoid loss. Examination of the blood of this animal proved it to be swarming with anthrax bacilli. Billings states that in the Bavarian Alps it is common for the farmers to conceal the presence of anthrax in their cattle and to dress the diseased animals for food, preserving the flesh in pickle. As spores do not form during life, nor after death unless the supply of oxygen is abundant, such flesh will contain vegetative bacilli for the most part, if not entirely, and these are readily destroyed in cooking.

External anthrax can unquestionably be conveyed by flies and other insects, though this is probably a rare method of infection.

Age.—Anthrax is practically confined to adults.

Sex.—The great majority of cases are in males, since women are much less often engaged in callings which expose one to infection. Among 261 cases in England, 224 were males and 37 females.

Bacteriology.—The bacillus of anthrax is one of the largest pathogenic bacteria. The individual rods are 1.2μ thick and 6 to 8μ long. The ends are characteristic, being square-cut or even depressed, so that in chains the elements are separated by a lens-shaped space. It forms

very long filaments in suitable culture media. It stains readily with the usual basic aniline dyes, and is not decolorized by Gram's method. Colonies on agar and gelatin are very characteristic. They are made up of wavy masses like locks of hair, radiating from the centre. The edges of growths on slanted agar present the same appearances. In bouillon, a delicate flocculent growth takes place, resembling bits of Japanese paper, or shreds of cotton suspended in liquid. Later, the growth tends to settle to the bottom. In gelatin stab-cultures the growth is equally characteristic. Radiating from the central puncture are innumerable very delicate spikelets pushing out into the gelatin, sometimes being spirals.

The bacillus grows best at 35° C. and ceases to grow below 12° C. or above 45° C. It owes much of its pathogenic power to its property of forming spores. This takes place best at 32° C., and the presence of oxygen is necessary. These spores are remarkable for their power of resistance to external agencies, such as heat, drying chemicals, etc., which destroy the vegetative bacillus readily. When dry the spores retain their vitality and virulence indefinitely, and it is through their agency that the disease is transported from distant parts of the world on hides and wool. Székely found the spores in dried cultures alive and fully virulent after eighteen and a half years.

Moist heat of 70° C. kills the bacilli in one minute, but the spores must be subjected to live steam or boiling for more than five minutes and to dry heat of 140° C. for at least three hours to insure their destruction. Cold has no effect on them. The writer has kept them immersed in liquid air at a temperature of 212° F. below zero for three hours without any perceptible effect.

They resist a 5 per cent. solution of carbolic acid always for two or more days, and sometimes for as long as forty days. Corrosive sublimate (1 to 1000) usually kills them in two hours, but Esmarch has found them to resist a 1 to 100 solution for three days, though virulence was lost in twenty hours. The resistance of spores appears to vary somewhat in different cultures, but is always very great. Unlike the vegetative organism, they are unharmed by the action of the gastric juice, and in cattle, where inoculation generally occurs through the digestive tract, are practically always the agents of infection.

The ordinary processes of tanning leather do not affect them injuriously. The writer has kept them immersed for two hundred and forty-four days in the strongest tanning fluids—twice the usual time required in the process—without any perceptible change in their vitality or virulence.

Spores are not found in cultures kept at temperatures below 18° C. nor above 42° C. Grown above 42° C. the bacillus loses the power of forming spores entirely, becomes gradually attenuated, and acquires vaccinal properties. When brought to this condition the attenuated bacillus can be cultivated at ordinary temperatures, without regaining virulence or the spore-forming power. The vaccines of Pasteur are prepared in this manner, the degrees of attenuation depending on the number of days the culture is kept at 42° to 43° C. The first, or weakest,

vaccine is grown for about twenty-four days, at the end of which time it has lost the power to kill larger animals, and even guinea-pigs, but will still kill white mice; the second vaccine is grown for about twelve days, and should kill guinea-pigs but not rabbits. In practice, an interval of twelve to fifteen days is allowed to elapse between the two inoculations, which are made subcutaneously.

Pathogenesis.—Practically all the domestic animals are susceptible. Fowls are refractory under normal conditions, but can be made susceptible by lowering their temperature. Dogs and cats are sometimes accidentally infected. The herbivora are most susceptible, the carnivora less so, although instances of the disease have been known in lions, tigers, bears, jaguars, etc. Man occupies an intermediate position in the scale of susceptibility.

The action of the anthrax bacillus has been the subject of much discussion, and is not yet thoroughly understood. Attempts to isolate the toxin have given very contradictory results, and no one has succeeded in isolating from cultures substances which produce the effects on animals of the living bacillus. Conradi doubts the production of a toxin. There can be little doubt that in the living body the bacillus elaborates bodies which either directly or indirectly are toxic. It is possible that in the body, substances are formed which are not elaborated in cultures.

Morbid Anatomy.—The body becomes quickly discolored—in two to four hours—and decomposition sets in early. The cellular tissues, especially about the neck and chest, become the seat of a putrid emphysema, sometimes with very great distension. From the mouth, nose, and other orifices, runs a dark, chocolate-colored fluid. The blood is fluid and almost black in color.

In rapid cases there may be only congestion of the lungs, ecchymotic spots on the pleuræ and pericardium, with a small amount of effusion, the liver and kidneys showing cloudy swelling and enlargement. Sometimes hemorrhages are found in the lungs, heart, kidneys, and other organs. In the majority of cases the lesions are more marked. They consist principally in serous or gelatinous effusions, sometimes blood-stained, into the tissues about the trachea, pharynx, root of the lungs, anterior mediastinum, and kidneys. These effusions are frequently seen also in the omentum and mesentery, in the subperitoneal tissues, and sometimes along the retroperitoneal glands. Large serous effusions into the pleuræ and pericardium are common. Less frequently the peritoneal cavity contains fluid. There is great enlargement of the bronchial glands, with ecchymoses and hemorrhages in and about them. The heart muscle is dark, soft, and flabby. The spleen is sometimes, but not constantly, enlarged, congested, and soft. When much enlarged the pulp is almost black and diffluent.

In pulmonary anthrax, Greenfield has made the most complete microscopic studies. He describes the characteristic lesion as occurring in the lower trachea and larger bronchi. The bacilli are found in large numbers in the mucous and submucous tissues, chiefly in the lymphatic vessels, and in the lymphatic plexuses around the arteries.

In intestinal anthrax the local lesions are found chiefly in the stomach

and small intestine. They appear as hemorrhagic areas, somewhat elevated, dark red in color, and surrounded by an œdematous, injected zone. The centre of the lesion is sometimes ulcerated or gangrenous. Bacilli are plentiful on the surface of the ulcerations and in the deeper structures.

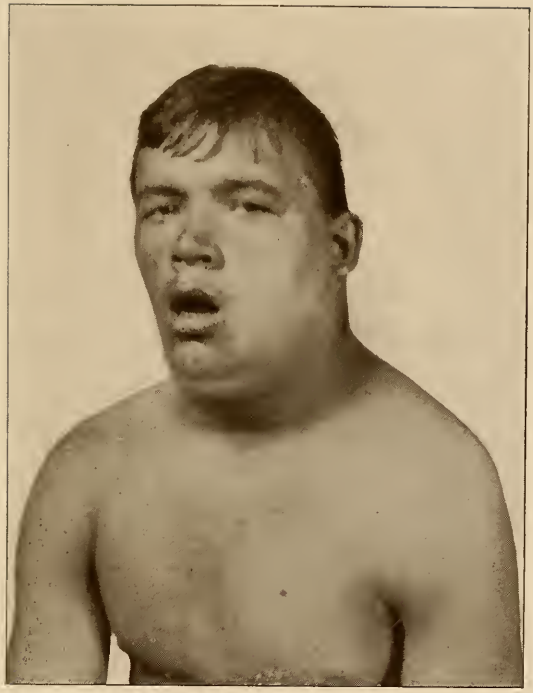
Malignant Pustule.—In the pustule are seen the various stages of an acute exudative inflammation, which may be serofibrinous, hemorrhagic, or necrotic. Davaine, who studied excised lesions two and three days old, found the anthrax bacilli at the centre of the pustule, situated in the rete mucosum, in closely packed groups, separated by normal epithelium, the initial proliferation apparently taking place in the deep layers of the epidermis. According to Strauss, the black eschar is strictly dermic, consisting of the papillary layer and upper portion of the derma. It is covered by a crust composed of coagulated amorphous exudate, and is separated from the underlying and living portions of the skin by a thick layer of embryonal cells, which form, as it were, a line of demarcation, in which the bacilli are found in very large numbers. The deeper skin and subcutaneous cellular tissues are distended by a seroalbuminous exudate, very rich in leukocytes. The infiltration is diffuse and not especially marked about the bloodvessels. The bacilli are found in the lymph spaces, not in the bloodvessels. In the neighborhood of the pustule, the papillary layer, the derma, and the subcutaneous tissues are the seat of an acute inflammatory œdema, with infiltration of the tissues by leukocytes and bacilli. In charbonous œdema, the bacilli are found exclusively in the subcutaneous cellular tissues—not in the skin, as in the malignant pustule.

Distribution of Bacilli.—In the lower animals the bacilli are found in the blood in enormous numbers. In man they are very much less numerous. They are always found in and near the point of inoculation, and in the lymphatic vessels to the nearest gland. They are generally found in the serum of the vesicles about the eschar, and sometimes in the œdematous tissues several inches away. In the late stages they may be found in the blood from the ear or fingers. They are generally present in the effusions into the serous cavities. When the kidneys are involved, the bacilli may pass into the urine. Sections of the various tissues and organs yield very variable results. Some bacilli can usually be found, and sometimes large numbers.

Symptoms.—1. **External Anthrax.**—(*a*) *Malignant Pustule.*—This is the most common form in man, and is the result of direct inoculation. It occurs almost always on those portions of the body which are habitually uncovered, such as the face, neck, and arms. The lesion is usually single, though two and even three points of inoculation have been observed. The period of incubation is from one to three days.

At the point of inoculation a small red papule with a central punctum appears, sometimes preceded and always accompanied by itching and burning. By the second day a flattened vesicle has formed, which may be surrounded by some redness and swelling. The vesicle soon ruptures and is replaced by a yellowish erosion, which rapidly becomes brown and, by the fourth day, a black, depressed eschar has formed, surrounded

PLATE XIII



Anthrax of Neck, showing Marked Œdema of Neck, Shoulders, and Breast; Fifth Day. (Royer, Therapeutic Gazette, 1908.)

by a very characteristic border of small vesicles. The circle of vesicles is slightly elevated, and may be complete or irregular. More or less numerous vesicles may appear on the neighboring skin. The eschar grows larger as well as deeper, and may attain a diameter of 2 to 3 centimeters. The subjacent and surrounding tissues are the seat of a hard œdematous swelling, which is often very extensive, involving an entire limb, the face, or a large part of the trunk. When the lesion is about the face, the deformity is very great. The neighboring lymphatics are sometimes involved, becoming tender and enlarged.

The freedom from pain in and about the lesions is remarkable. Even when very extensive, the patient complains only of a sense of weight and fulness, with some tenderness on pressure. Pus is never formed until the eschar begins to separate—from the ninth to the fifteenth day.

The general symptoms are very variable, and bear no relation to the extent of the local lesion. In severe cases the symptoms indicating general infection come on within twenty-four to thirty-six hours; in other cases not for some days or even a week. The early symptoms are lassitude, malaise, headache, chilly sensations or slight rigors, loss of appetite, perhaps vomiting, restlessness, and disturbed sleep. Fever may be absent and is usually not marked. The temperature is not an index of the gravity; it may be high in favorable and low in fatal cases. It frequently falls before death. The pulse may not be affected at first. It is usually more frequent, but soft. With an increase in the symptoms, it becomes weak, rapid, and intermittent.

Among the later symptoms may be persistent vomiting, fetid diarrhœa, a sense of oppression, with rapid breathing and a tendency to cyanosis; delirium, coma, or convulsions, according to the internal localization of the infection. Consciousness is usually retained until the end. Death is sometimes sudden, with no premonitory symptoms.

(*b*) *Malignant Anthrax Œdema.*—This is seen chiefly about the eyelids, though it may occur about the lips, neck, and trunk. There is no characteristic eschar. The swelling may be very great and consists of a diffuse, painless, semitransparent œdema, soft at first but growing harder as it increases. Vesicles may form on the surface, which are followed by eschars, similar to the ordinary malignant pustule. The course of the disease is more rapid and more fatal than in the ordinary form.

2. **Internal Anthrax.**—(*a*) *Intestinal Anthrax; Mycosis Intestinalis.*—This mode of infection is rare in man, but the usual one in cattle. The onset is sudden. There may be prodromal symptoms, such as malaise, weakness, headache, chilliness, sweats, etc. Gastro-intestinal symptoms come on rapidly. There is complete anorexia and thirst, soon followed by nausea, persistent vomiting, diarrhœa—which may be bloody—and marked abdominal pain. The symptoms have been mistaken for strangulation of the intestine. The abdomen becomes distended, the respiration rapid, dyspnea is often considerable, due partly to areas of congestion in the lungs, or to pleural effusions, the pulse becomes rapid and small, the skin cold and clammy, the face cyanotic.

The temperature is seldom high and usually only slightly above normal, often falling and becoming subnormal before death. The

patient is profoundly adynamic and dies in collapse, retaining consciousness to the last; or else delirium, convulsions, and coma may precede the end. Death may take place in thirty-six to forty-eight hours, the symptoms resembling those of acute gastro-intestinal poisoning. The usual duration is five or six days.

(*b*) *Pulmonary Anthrax; Woolsorters' Disease; Anthracemia.*—In this the symptoms may be vague and slight until just before death, and even then the patient may not feel particularly ill. The patient may feel so little disturbance that no apprehension is felt, until suddenly he goes into collapse, becomes cold, pulseless, and dies within a few hours. The initial symptoms are malaise, slight chilliness, or shivering, a sense of extreme weakness and fatigue, and uneasiness about the chest and stomach. Vomiting occurs in about one-half of all cases, and may be persistent. Diarrhœa is less frequent.

The lungs are always involved. There is a sense of constriction or oppression in the chest, with rapid and difficult breathing. Cough is generally present but seldom very annoying. The sputum is seldom abundant and may contain blood or be rusty. Anthrax bacilli are sometimes found in it. The percussion sounds are often clear; impairment when present is usually on the right side. Moist rales may be heard. The right lung is more frequently and more extensively involved, as a rule, than the left.

The temperature is seldom very high. The pulse may not be much altered until late in the disease. As a rule, however, it is rapid and weak out of proportion to the apparent severity of the condition. Toward the end it becomes small, irregular, and rapid. The urine is scanty, dark, and of high specific gravity—1040 in some cases. It often contains albumin, but seldom in large quantity. The duration varies greatly. Death takes place, in the majority of cases, on the second, third, and fourth days. Bell has reported fulminating cases with death in seventeen hours.

Diagnosis.—In all forms of anthrax the occupation of the patient should excite suspicion. Malignant pustule is almost always on some part of the body habitually uncovered. It is distinguished from furuncle and carbuncle by the absence of pain and suppuration. The absence of pain will serve also to differentiate it from phlegmonous erysipelas and cellulitis. When the lesion is fully developed the central, black eschar with the "brawny œdema," and surrounding vesicles are so characteristic that mistakes can hardly be made.

Intestinal anthrax is so much like other forms of acute gastro-intestinal poisoning that diagnosis may be impossible. There may be œdema about the root of the neck, which, with the occupation, may furnish a clue. Anthrax bacilli have been found in the serum before death.

Pulmonary anthrax is impossible to diagnose in the early stages. Bell says that the slightest illness in persons exposed to infection should be looked upon with suspicion until the possibility of anthrax is excluded. In cases which are not very rapid, and complicated with pleurisy and pneumonia, great prostration, with a weak, rapid pulse, not accounted for by the local lesions, should attract attention. Diagnosis is difficult.

Prognosis.—This is bad in all forms. Cases in which the onset is marked by decided symptoms and a temperature above 102.5° F. are more favorable than those in which the symptoms are vague. The active symptoms indicate reaction on the part of the patient. The danger from malignant pustule varies with its site. Lesions on the neck are the most dangerous, on account of œdema of the larynx, and involvement of vital organs. Lesions on the eyelids are also especially fatal. Limitation of the lesions by marked inflammatory reaction about them is a favorable indication. Fever is more favorable than a low or subnormal temperature. Bell considers the pulse the best guide; when full and moderately rapid, the prognosis is hopeful. The outlook is bad when the pulse is small, weak, and rapid.

In the past, pulmonary anthrax has been regarded as almost necessarily fatal. Dr. Mitchell,[1] of Bradford, England, whose extensive experience gives great weight to his opinions, protests against this view. Bacilli are usually absent from the general circulation until within twenty-four or thirty-six hours before death. He regards cases as curable up to this point. He has seen many suspicious cases, and some presenting all the symptoms of pulmonary anthrax recover under the use of Sclavo's serum.

Treatment.—Malignant pustule begins as a local infection, and for some days the bacilli are localized in and near the local lesion. Destruction of the pustule is therefore indicated, and it is of great importance that it should be practised at the earliest possible moment. When done before the bacilli have invaded the lymph channels and bloodvessels, a favorable issue may usually be confidently looked for. The actual cautery and excision with the knife are the two procedures most to be recommended. In either case extirpation must be thorough. When excision is contemplated, the danger of rapid generalization of the infection must be considered. Reports state that œdema rapidly followed excision so closely in some cases, and generalization in others, that there was almost surely some connection between the operation and the symptoms. After excision with the knife, which must include the tissues for at least a half-inch beyond the eschar, the wound should be well swabbed with carbolic acid. Injections of carbolic acid should be made into the tissues at five or six points around the wound and repeated at intervals of four hours if the symptoms are urgent. Bell advises for this purpose 15 minims of a 5 per cent. solution of carbolic acid in equal parts of water and ether. Over the whole should be applied an antiseptic dressing and an ice-bag.

In Europe the actual cautery and chemical caustics are preferred. Ascoli advises the actual cautery strongly. It must extend into the healthy tissue around and beneath the pustule. Extensive scarring may result, but the operation is free from the danger attending excision. Among chemicals, caustic potash is highly recommended. Graef has collected a series of 384 cases treated with caustic potash by himself and others, with only 20 deaths. Muskett regards powdered ipecacuanha as

[1] *British Medical Journal*, 1911, i, 750.

having a specific action, using it as a dressing and also giving it internally. He treated 50 cases without a death in this manner. At Guy's Hospital, London, it is much used, although excision is first practised. The dose is 10 grains, given every three hours. The general treatment is supporting and stimulant.

There is little to be offered in the way of treatment in pulmonary and intestinal anthrax. Indications must be met and the patient's strength kept up so far as possible by nutritious foods and stimulants.

Serum Treatment.—Marchoux,[1] in France, and Sclavo, in Italy, independently demonstrated in 1895 the possibility of producing a specific serum which is both prophylactic and curative, the former using rabbits and sheep, while Sclavo now uses the ass. Sclavo begins his immunization by injecting attenuated cultures of anthrax at intervals of ten or twelve days. Later virulent cultures are used in increasing doses. After prolonged treatment the animal is bled, and the serum tested on rabbits. A number of rabbits are inoculated with the same dose of anthrax bacilli. Half of the number inoculated receive 10 cc. of the serum to be tested, while the others are kept as controls. If all the controls die and the protected animals live the serum is considered as high grade.

The serum appears to stimulate phagocytosis—it is antibacterial, and, according to some observers, antitoxic. The serum should be used freely. The dose is 30 cc. to 40 cc. injected under the skin of the abdomen, preferably in amounts of 10 cc. in different places.

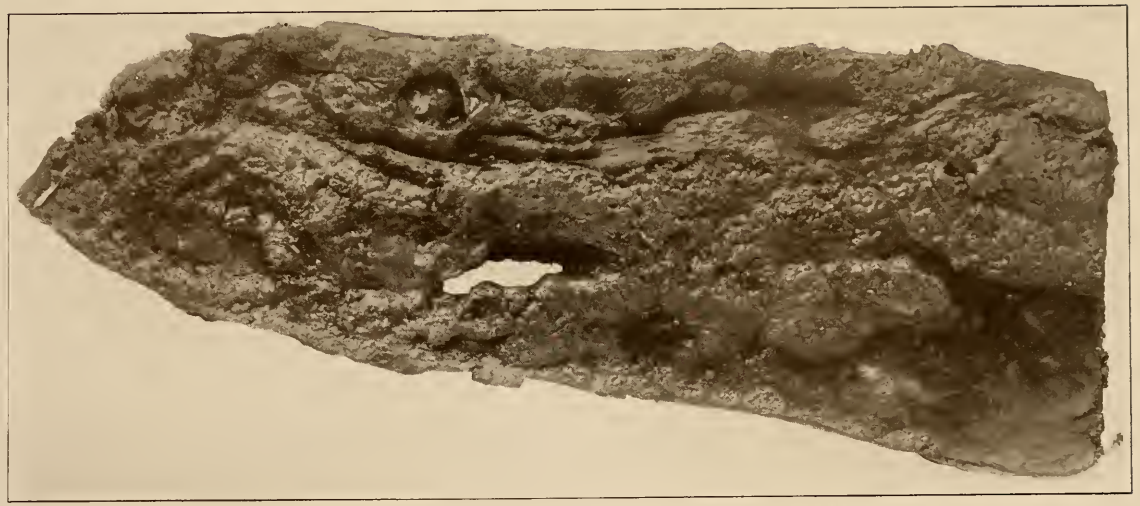
Ascoli, surgeon to Pacchetti's Horse-hair Works in Milan, uses serum extensively, often as the only treatment. He injects it intramuscularly and intravenously, often alternating the methods in the same patient. The intravenous dose is from 5 cc. to 15 cc. He may repeat the injections five to six times in the same day, being guided by the severity of the symptoms. In severe cases he gives digitalis also. Statistics of 164 cases treated with the serum give a mortality of 6.09 per cent. The average duration of treatment, estimated from 44 cases in which the data were precise, was eight days. Marked improvement was usually observed by the third day. Serum is now extensively used in England, with results which appear to be excellent. In America it has been employed with marked success by Royer and Holmes. The earlier the employment of serum the more favorable is the result.

Preventive Measures.—It is difficult to carry out efficient preventive measures. In some countries where anthrax is very prevalent, such as China, there is no way of getting reports of the existence or extent of anthrax, and no method of preventing the shipment of hides and hair from diseased animals packed with healthy material.

Many attempts have been made to disinfect hides and dangerous fleeces, but most of them have resulted in injury which impaired the commercial value. The "formic mercury" process of Seymour-Jones[2] has been carefully studied by experts in England and is recommended by high authorities. It consists in placing the dried hides and skins for

[1] *Annal. de l'Institut Pasteur*, 1895.
[2] Ponder, Report to Worshipful Company of Leathersellers, 1911.

PLATE XIV



Glanders. Erosion of Nasal Septum in Horse.

twenty-four hours in a soak containing 1 per cent. formic acid and 0.02 per cent. bichloride of mercury, after which they are transferred to brine. They thus rapidly become "wet salted," by which the danger of dust is done away with. Bacteriological tests indicate that anthrax spores are largely destroyed, and the hides rendered practically safe. Porters and others handling dry hides should be required to have the arms and neck covered, and to wear gloves. In England, woolsorters' disease has been lessened by regulations requiring that dangerous wools and hairs shall be steeped and washed in hot suds and sorted while damp. In other cases the sorting is done over wire screens provided with suction apparatus. The dust collected is burned. All skin, clippings, and bags which have contained dangerous materials are disinfected before being sold. Operatives with sores or cuts are not allowed to work, and appliances for disinfecting and treating wounds are kept on hand.

GLANDERS

Synonyms.—Greek, Malis; Latin, Malleus, Equinia; English, Farcy; French, Morve, Farcin; German, Rotzkrankheit, Wurmkrankheit.

Definition.—Glanders is a specific contagious disease of solipedes caused by the *Bacillus mallei*, and transmissible to man by accidental inoculation. The disease assumes two forms: an internal, to which the name glanders is applied, and an external, which is known as farcy.

Glanders in the Horse.—The disease assumes two types, glanders proper and farcy, though they may coexist. In glanders the septum of the nose and neighboring tissues are chiefly affected. Nodules, which are firm and translucent gray in appearance, form in the mucous membrane, accompanied by inflammation and a catarrhal discharge. The nodules soften and break down, leaving irregular ulcers. The glands in the neck, mediastinum, etc., are usually involved. Nodules are always found in the lungs, with areas of congestion, and quite often in other organs. In farcy the disease affects chiefly the superficial lymph vessels and glands, which become irregularly thickened and hard, forming the so-called "farcy pipes" and "farcy buds." Softening and suppuration usually take place and ulceration follows. Secondary deposits often occur in the nasal mucous membrane and in the internal organs. Farcy is apt to run a more chronic course than glanders. The bacilli are found in the nasal discharge and in the suppurating lymph glands, and contagion is usually due to these discharges. Under natural conditions glanders also affects mules and donkeys. The mule is more susceptible than the horse, and the donkey the most susceptible of the three. Menagerie animals contract glanders from the flesh of glandered horses.

Etiology.—Glanders in man is almost always contracted from the horse, and is therefore practically confined to men whose occupation brings them into constant contact with horses, such as hostlers, drivers, farmers, veterinarians, knackers, etc. It has been contracted by drinking from the same bucket, or using a cloth with which the nose of a glandered horse had been cleansed. The disease is practically confined

to men. In 120 cases, Bollinger found only 6 women. Transmission of glanders from man to man is not uncommon. Robins[1] in a study of 156 cases found 15 which were directly associated with other human cases. Eleven cases of this series were women, 6 of whom were infected directly or indirectly from human cases.

All affected tissues contain the bacillus, and are virulent; the discharge from the nostrils is perhaps the most frequent medium of contagion. The saliva is sometimes virulent from admixture with the nasal discharge. The blood rarely contains the bacillus and when present it is in small numbers. They pass into the urine not infrequently. Infection takes place most commonly through some abrasion. Mere deposit of matter containing the bacillus on the healthy skin is probably harmless. The bacillus apparently penetrates the nasal mucous membrane quite readily. Small animals are easily infected by the simple deposit of virulent material in the nose. The conjunctiva is more resistant. Infection through the digestive tract takes place readily in horses, the resulting lesions appearing first in the lungs, as a rule. Infection through the deeper respiratory tract appears to be rare. Glanders has proved very fatal to bacteriologists, a number of whom have lost their lives through accidental infection.

Bacteriology.—The bacillus was discovered by Loeffler and Schutz in 1882. It is quite irregular in form and size, being 2 to 5μ long and 0.5 to 1μ thick. It stains readily, but not deeply, with the ordinary aniline dyes, and gives them up just as readily, hence it is difficult to stain in sections of tissue. It does not stain by Gram's method. It stains unevenly, presenting a beaded appearance. It is aërobic, non-motile, and does not form spores.

Growth takes place at 25° to 42° C., but best at body temperature. It grows readily on most of the ordinary culture media when once isolated. For isolation, blood serum and glycerinated potato are the best media. The growth on potato is especially characteristic. By the third day a yellowish honey-like growth is seen, which spreads and becomes darker, so that by the eighth day it is reddish brown or chocolate colored. The bacillus soon loses its virulence in cultures, and must be passed through a susceptible animal in order to keep it up.

The presence of the bacillus is generally determined by the intraperitoneal inoculation of male guinea-pigs. If it is present, in two to three days there is observed a marked swelling and redness of the testicles. Pure cultures are readily obtained from the testicles a few days later.

Mallein is an extract of the glanders bacillus containing the specific toxin, prepared by growing the organism for four to six weeks in 5 per cent. glycerine bouillon. It is then sterilized, evaporated to one-tenth of the original volume, and filtered through porcelain to remove the bacilli. Before use it is diluted in a 1 per cent. solution of carbolic acid. When injected into glandered animals it produces a definite reaction.

Morbid Anatomy.—Glanders is usually classed among the infectious granulomata. Lesions may be found in almost every portion of the

[1] *Studies from Royal Victoria Hospital*, Montreal, 1906, vol. ii, No. 1.

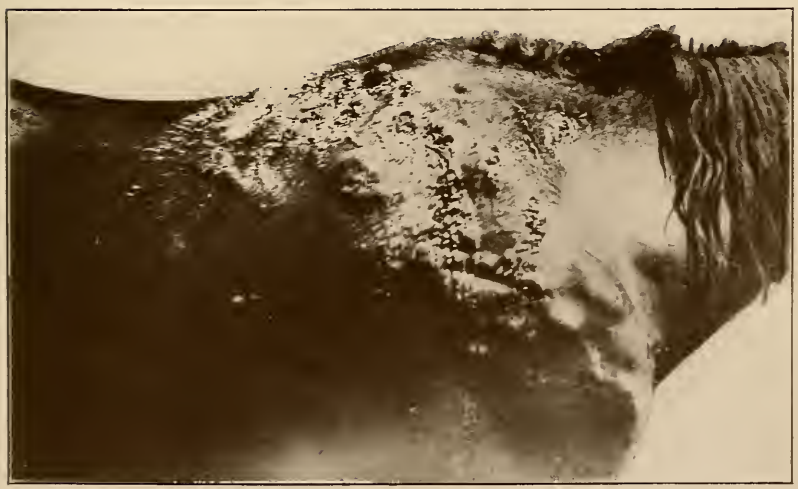
PLATE XV

FIG. 1

Acute Human Glanders.

(Zeit, in Journal of the American Medical Association.)

FIG. 2



Farcy Affecting Skin of Shoulder of Horse.

(Bureau of Animal Industry.)

body. Superficially we find the various pustules, abscesses, and ulcers, with more or less extensive areas of erysipelatous and phlegmonous inflammation, all of which are apt to be about the face and limbs. These have the general appearance of the suppurative lesions common to different forms of pyemia, and are especially characteristic of human glanders. A characteristic feature is the rapidity with which nuclear fragmentation occurs, and the persistence with which the fragments remain as deeply staining debris. Liquefactive necrosis of the leukocytes and tissues may occur, so that on incision of a focus only an oily fluid (farcy oil) comparatively free from cellular elements may be found (McFadyean, quoted by Robins). The mucous membrane of the nose is covered with a viscous mucopus, under which are found ecchymoses, pustules, and ulcers. The latter, especially in chronic cases, may expose the cartilages and bones, which are necrotic. Cicatrices, which are frequent and extensive in the horse, are rarely found in man. Similar changes are found in the frontal sinus, the pharynx, larynx, and trachea. The joints frequently contain serous, serosanguinolent, or purulent fluid. Osteomyelitis and periostitis may be present, or there is more or less extensive necrosis of denuded bone. All of the internal organs may contain nodules. They are rarely absent from the lungs, being scattered throughout, but are most numerous under the pleura. They vary much in size. Wright regards the lesion as essentially a focal pneumonia, with suppuration and necrosis. In chronic cases a capsule may be formed, as in the horse, and the central area becomes caseous, and, in the horse, even calcareous. The serous cavities often contain serum and blood. The spleen is large, soft, and filled with blood. The kidneys are rarely affected. The liver shows fatty degeneration and metastatic abscesses.

Incubation Period.—This is uncertain. In the majority of cases it appears to be from one to five days.

Symptoms.—These vary with the form of the disease, which may be glanders or farcy, both of which may be acute or chronic. Acute glanders does not pass into the chronic type, but frequently the chronic form ends in an acute outbreak.

Acute Glanders.—The first symptoms may be chills, marked weakness, headache, anorexia, epistaxis, accompanied by more or less intense pains about the joints, which are more severe at night. As a rule, however, local symptoms appear before the general phenomena. The face, hands, and feet may become swollen and hard. The lymphatics become inflamed, forming hard cords, tender on pressure, and the corresponding glands grow large and painful. Phlebitis is sometimes observed. In fine, the early symptoms are those of pyemia. After two or three days an erysipelatous condition appears about the face, and sometimes in the limbs or about the joints. The nose, lips, cheeks, forehead, and even the scalp are swollen and discolored. Soon afterward a pustular eruption appears over these areas, somewhat resembling smallpox. The pustules are, however, pointed or flat, and not umbilicated. They are usually discreet, but may become confluent, forming purulent plaques. Bullæ containing serosanguinolent fluid are often met with, which

rupture, leaving foul ulcers, or else, by drying, crusts. Gangrene of the skin often occurs on the seat of these lesions, or follows the extravasation of blood into the cellular tissues. Under the gangrenous skin large collections of pus form, and, if life is prolonged sufficiently, the separation of the sphacelus may lay bare the tendons and even the bone.

In many cases, following the pains in the joints, hard tumors appear in the muscles on both sides of the body, which suppurate and discharge, often pointing beneath the bullous patches. With the cutaneous eruption the characteristic nasal symptoms appear, preceded by a sense of discomfort and obstruction in the nose and nasopharynx. Soon there appears an abundant mucopurulent, viscous discharge, often streaked with blood, which causes excoriations of the lip. Examination of the nose shows the mucous membrane to be red, excoriated, and often ulcerated. Pustules and ulcers may be found on the tonsils, pharynx, and larynx. The cervical and submaxillary glands enlarge, and sometimes suppurate.

A metastatic lobular pneumonia supervenes and hastens the end. Cough becomes harassing and dyspnœa marked. Impairment of resonance and rales are found, especially at the base of the lungs.

The temperature is not much elevated at first; later it may reach 104° or 105° F. The morning remission is marked. The pulse is rapid and weak. There is often a fetid diarrhœa. The urine contains albumin and sometimes blood. The mind is sometimes clouded early in the disease, and stupor, deafness, delirium or coma, may come on rapidly. Death may occur with coma or convulsions.

Chronic Glanders.—This form is met with usually as a sequence of chronic farcy, the nasal and respiratory symptoms coming on after a variable time, two to six months, though sometimes the type is chronic from the outset. Diagnosis is very difficult in these cases. The early symptoms are much the same as in the acute type, malaise, fatigue, pains in the muscles and joints. The mucous membrane of the nose and throat soon becomes involved. The nose becomes more or less occluded, and sometimes there is severe pain about the root of the nose, passing up toward the frontal sinuses. A mucopurulent discharge appears, often streaked with blood and containing crusts and small blood-clots. Occasionally the discharge is abundant; again so slight that the nasal involvement may pass unobserved. Examination of the nose reveals ulcerations, sometimes exposing the bone, or even perforating the septum. Ulceration of the mouth, palate, and larynx may also be found. The voice is altered and deglutition difficult. Cough is very annoying. Often there is pain along the trachea and behind the sternum, with tenderness on pressure. Involvement of the lungs is manifested by dyspnœa, frequent cough, with thick, grayish, blood-streaked sputum, profuse sweats, emaciation, and exhaustion.

The other general symptoms are identical with those of chronic farcy —pains in the muscles and joints, neck, and loins, diarrhœa, nausea, irregular chills and fever, sweats, and progressive emaciation.

The course is slow, and remissions occur. Life may be prolonged for as much as six years, but cure seldom or never takes place.

Acute Farcy.—Acute farcy differs from acute glanders chiefly in the absence of involvement of the nasal mucous membrane. The general symptoms are much the same, chills, headache, nausea, and vomiting, with pains in the muscles and joints. The local symptoms are those of a poisoned wound. The point of inoculation becomes an unhealthy looking ulcer, the lymphatic vessels and glands become inflamed, tender, and enlarged. The limbs become œdematous and erysipelatous. About the sixth or seventh day multiple abscesses begin to form in various parts of the body without relation to the point of infection. These may appear as inflammatory tumors, hard, tender, red or purplish in color, opening like furuncles, or as indolent, soft swellings, with no reaction of the skin and surrounding tissues. They contain usually a serosanguinolent fluid, rarely pus, and result in the formation of ulcers. Besides these, large collections of pus form in the cellular tissues. The general condition of the patient is aggravated at the same time; there is marked fever and profound adynamia. About the third or fourth week a pustular eruption appears, which may be widely distributed over the face, limbs, and body. The eruption is often accompanied by gangrene. From this point the symptoms are identical with those of acute glanders, though life is more prolonged. Delirium and coma supervene about the fifth or sixth week, sometimes in the third or fourth, and end in death.

Chronic Farcy.—Chronic farcy is more common than chronic glanders. The mode of onset is variable. Ordinarily it follows direct inoculation, with local manifestations of a poisoned wound; inflammation of the lymphatic vessels and glands appears in three or four days, accompanied with fever, nausea, and vomiting. In other cases the onset is very acute, with headache, nausea, high fever, and delirium, these symptoms subsiding after three or four days. Again the onset is very insidious and slow. There are vague pains in the limbs and joints, with difficulty of motion. There is loss of strength and vigor without apparent cause. After four to six weeks multiple abscesses form in the muscles or subcutaneous tissues, especially in the legs and about the joints. They are usually not painful, and there is no marked reaction in the skin and surrounding tissues. The skin over them becomes purplish after a time. Their size is variable, some containing as much as 500 cc. of fluid, which may be blood, or blood and pus mixed. Laudable pus is rare. These collections may persist for six to eight months, opening externally finally, or sometimes being absorbed. Less frequently phlegmonous abscesses are met with, which form and open rapidly, discharging pus. The rupture of the abscesses leaves fistulæ which sometimes persist for a long time discharging an oily or gummy fluid, at other times healing rapidly. Successive crops of abscesses may follow each other for a long time, the patient becoming more or less emaciated and feeble.

The symptoms often abate and even disappear, so much so that cure may seem complete, but after a variable time, usually thirty to sixty days, relapse occurs and the disease resumes its course. Pains in the joints and various parts of the body come on, digestive disturbances appear, marked by nausea and sometimes vomiting. The abscesses for the most part now leave fistulæ or ulcers. Emaciation progresses

rapidly, the skin becomes dry, hectic fever with chills and night-sweats comes on. There is a persistent and fetid diarrhœa. A dry cough is often present. The patient falls into a delirium which may end the scene. More often acute glanders supervenes, and rapidly terminates life.

Diagnosis.—This is difficult, except in acute cases where the history of inoculation is clear. The symptoms following inoculation resemble closely those of any poisoned wound, the chief difference being that in glanders the period of incubation is usually three or four days, while in other forms, especially those due to streptococcus infection, the incubation rarely exceeds twenty-four hours. As soon as pus is formed, a bacteriological examination should be made. The presence of the glanders bacillus is best determined by the intraperitoneal inoculation of male guinea-pigs.

In all cases the occupation should receive careful attention, though it is often very difficult to trace any exposure to a glandered animal.

The eruptive stage may resemble smallpox. The glanders pustules appear in successive crops and ulcerate rapidly. They are not umbilicated and not so uniform as variolous pustules. The chronic type may offer special difficulties, as certain types of syphilis closely resemble it. Even the destructive changes about the nose are simulated. The differentiation may rest on the effect of specific treatment.

Serum Diagnosis.—M'Fadyean has shown that the serum of glandered horses agglutinates the *Bacillus mallei* in dilutions as high as 1 to 1600. The reaction is well-marked in dilutions up to 1 to 1000. Normal horse serum agglutinates slowly in dilutions up to 1 to 300. The cultures are grown in bouillon, and should not be more than two or three days old.

Precipitin Test.—This is best carried out after the method of Konew.[1] Antigen termed "mallease" is prepared by dissolving cultures of the glanders bacillus in antiformin, and neutralizing with a 5 per cent. solution of sulphuric acid. Approximately equal parts of mallease and blood serum from the suspected animal are placed in a narrow test-tube, care being taken to avoid mixing. If the case is positive a ring of white cloudiness appears at the point of contact of the two layers of fluid.

Complement-fixation Test.—Of all diagnostic tests this appears to be the most accurate and delicate. A sheep-rabbit hemolytic system is usually employed, with guinea-pig complement. Antigen is prepared by suspending cultures of the glanders bacillus in normal salt, heating to 60° C. for four hours, and shaking in a machine for four days. The bacilli are removed by centrifugalization for two hours. The antigen is preserved by adding 10 per cent. of a 5 per cent. solution of carbolic acid. It remains active two to three months in a cool, dark place.

Prognosis.—The outlook is bad in every form of glanders. Acute and chronic glanders and acute farcy are practically always fatal. Chronic farcy sometimes ends in recovery. The remissions which occur may mislead one. Hallopeau and Jeanselme have reported one case in which the remission persisted three years, new abscesses then appearing

[1] *Centralblatt für Bakt.*, Abt. 1, Orig., 1910, Band lv, Heft 3.

and the case resuming its course. Robins believes that 6 per cent. represents approximately the number of permanent cures.

Treatment.—If seen early enough, the seat of inoculation should be laid open and thoroughly cauterized, preferably with the actual cautery. To be of value this should be done not longer than one hour after inoculation.

The treatment of the declared disease is local and general. Abscesses should be opened as they appear, evacuated and swabbed with a solution of chloride of zinc 1 to 10, or other strong antiseptic, then dressed with iodoform. Ulcers should receive the same treatment. Curettage has been advised before the application of the zinc. The thermocautery is strongly advised in the treatment of local lesions, sinuses, etc. The nose may be washed out with permanganate of potash or boric acid solution, followed by insufflations of iodoform or aristol.

The general treatment is tonic and supportive. There is no specific nor any drug that appears to have any special value. The best results seem to have been obtained from the use of sulphur and iodine in various forms. Bendall recommends benzoate of soda at frequent intervals. Nocard, M'Fadyean, and others believe that they have observed some curative effect of mallein in horses, but this is strongly contradicted. Babes and Bonome have used it in chronic glanders in man in doses of $\frac{1}{15}$ to $\frac{1}{20}$ of a cubic centimeter, with apparently good results. Vaccines, both stock and autogenous, have been tried in a few cases with results which appear to have been excellent. Great care must be taken with the discharges, soiled linen, etc., of patients, which should be destroyed by burning. If this is not possible, they should be disinfected by boiling. Attendants should be warned of the danger from the nasal discharge and the pus from the eruption, ulcers, and abscesses.

CHAPTER XV

WHOOPING COUGH

By JOHN RUHRÄH, M.D.

Definition.—Whooping cough is a contagious disease characterized by a paroxysmal or spasmodic cough usually ending in a long sonorous inspiration and frequently accompanied by vomiting. Cullen's famous definition was, "Morbus contagiosus, tussis convulsiva strangulans cum inspiratione sonora iterata, saepe vomitus."

Etiology.—Epidemics vary greatly from year to year in virulence, intensity, and mortality. The disease is more severe and frequent in cold climates; otherwise epidemics are apparently unaffected by season and weather conditions, although the course is less severe in weather which permits children to be outdoors. Epidemics of great severity and mortality have been seen in the summer. Susceptibility is very general, and the majority of persons have the disease. The greatest predisposition is from six months to five years of age, and over half the cases occur during the first two years of life. As the individual grows older the susceptibility decreases; but the disease is seen in adults and even in old age. During the first months of life the disease is not common, although it may be seen, even in the newly born. Watson records a case where the mother had been taking care of a child with whooping cough and her own child showed symptoms of the disease on the first day. Bouchut observed a child who had a cough on the second day and showed unmistakable signs of whooping cough on the eighth day. Girls are said to be more susceptible than boys, and children weakened by disease are more liable than strong healthy ones; the disease is more severe in the weak. In nervous children the paroxysms are always more severe. Wimmer and Meissner state that the deaf and dumb and the blind have the disease in a milder form.

Bacteriology.—Bordet and Gengou have described an organism which they call the *Bacillus pertussis* which is generally regarded as the cause of the disease. This organism is found in the mucous membranes from the respiratory tract but chiefly from the remoter parts, more often below the larynx than above it, and it is more abundant at the beginning of the whooping period than later on. If cultures are taken only from the upper part of the respiratory tract the organism may be overlooked as it grows very slowly in the first cultures, two or three days elapsing before colonies appear, and unless there is almost a pure culture it will be overgrown by other germs. Klimenko and Fraenkel claim to have produced whooping cough in monkeys. Wollstein has demonstrated this organism in the sputum in many cases but was unable to isolate it after the second week in most instances. The blood of whooping cough

cases agglutinates this organism. Delcourt has applied the Bordet-Gengou hemolytic reaction and believes there are cases in which the disease may be overlooked which can be demonstrated by this test.

Jahn and others called attention to the fact that domestic animals may be affected by whooping cough and may be the means of transmitting it to children. It is most frequently observed in dogs, but has also been noted in the cat.

The disease is usually transmitted by direct contact, and only a very short exposure is necessary for infection. In some instances it would seem that being in the immediate neighborhood without direct contact was all that was necessary; but in these the child may have been infected by flying particles of sputum. The infectiousness begins with the earliest symptoms, and is more intense early in the disease than later, although it may be transmitted even in the late stages. Morse attempted to determine whether the disease was transmitted by indirect contact by gathering the experience of forty observers. The consensus of opinion was that it happened but rarely. That transmission by fomites is possible is instanced by the following classic case: A woman whose two children had whooping cough was on a ship which touched at St. Helena, and the children's clothing was sent ashore to be washed. The children of the washerwoman contracted the disease, although there was said to be no whooping cough on the island at that time.

Infectiousness varies in hospitals and is most liable to occur when the patient enters early in the course. If the children mingle together indiscriminately, especially where there is overcrowding, an epidemic is sure to occur. If the beds are far apart, with plenty of air space, and the children are kept separated, the liability to infection is much less. If the sputum is carefully looked after, infection may be avoided.

Recurrences are rare, although clinicians of large experience may see one or two such instances; for example Rilliet and Barthez report 2 cases, Trousseau 2, and Comby 1.

The incubation period is difficult to ascertain owing to the indefiniteness of the early symptoms. From one to two weeks usually elapse from the time of infection to the onset, but this may be considerably less. If sixteen days pass and the disease has not made its appearance, the chances are that it will not develop.

Pathology.—There is more or less congestion and catarrhal inflammation of the mucous membranes of the larynx, trachea, and bronchi, and the severe coughing may produce emphysema. The lower surface of the epiglottis is also involved by the inflammation. The coughing frequently produces a small ulceration of the frenum of the tongue in children who have cut their teeth. The fatalities are caused by complications such as convulsions or pneumonia.

Symptoms.—Whooping cough has three stages: *i. e.*, a catarrhal stage or the invasion, a paroxysmal or spasmodic stage, and the stage of decline or defervescence.

Catarrhal Stage.—The invasion is general. The child has a slight bronchitis, which cannot be distinguished from an ordinary cold, often complains of headache or of general malaise, and there is often coryza,

with sneezing and increased lacrymation There may be photophobia and dilatation of the pupils. There is often a slight rise in temperature toward evening, but this usually ceases before the spasmodic stage begins. There may be muscular pains of considerable severity. The catarrhal stage lasts from one to two weeks and then passes into the spasmodic stage. Some children whoop almost from the beginning; others may not do so for over two weeks, and some not at all. There may be occasional paroxysms of coughing during the catarrhal stage, and a persistent cough, especially at night, should always arouse suspicion.

Spasmodic or Paroxysmal Stage.—The fever and catarrhal symptoms disappear, the cough becomes more and more paroxysmal, and in nearly all cases the characteristic long inspiration or "whoop" is heard. The child usually feels a paroxysm coming on, either in an indefinite way or there may be a sense of constriction about the chest or of oppression about the heart. The child runs to the mother or nurse for support, or grasps the nearest object, and if there is nothing near, both hands grasp the legs near the knees to brace the body for the approaching attack. There is a severe barking cough often of a loud metallic character, the face becomes reddened and cyanotic, the eyes are suffused, and the veins of the neck and head stand out prominently. All the muscles of the chest are brought into action. During the coughing there is protrusion of the spoon-shaped tongue. After a series of explosive coughs, there is the prolonged noisy whoop, and after one or several of these a small ball of tenacious mucus is expelled, very frequently with vomiting. In adults the paroxysms are less severe as a rule, although at times they may be very troublesome. The anxiety at the beginning of the spasm is not so marked, but in neurotic patients it may be as great as that in children.

The average number of paroxysms is about twenty in twenty-four hours (Trousseau). Tissier records a case in which in a three-year-old child on the seventh day there were one hundred and twenty paroxysms. The duration varies, and it may last only a few seconds, with a single whoop, or be prolonged for as much as fifteen minutes, with between fifteen and thirty whoops. The paroxysm may be brought on by excitement and irritation of various kinds. The attacks, as pointed out by Heberden, are less frequent in good weather than in bad. Attacks which come on after eructation, vomiting, or the passage of flatus, are lighter than usual, but the succeeding paroxysm is of usual severity. Cough of a paroxysmal character may be caused by imitation, and a whole school may be set to coughing by a patient with pertussis. In a ward full of whooping-cough patients all may cough at the same time, a paroxysm in one child bringing it on in the others. The whoop may be entirely absent and the cough merely of a paroxysmal character, as is common in young infants. The whoop may also vanish with the appearance of inflammatory diseases, notably pneumonia, meningitis, and diphtheria. Vaccinia is said to have the same effect.

The paroxysms may cause hemorrhage, or the sphincters may relax with involuntary passage of urine or feces. After the attack the child may be utterly exhausted and remain in a half-conscious condition;

others have a fit of crying; sometimes after the paroxysm the child may be at once ready to return to play. Cases have been reported where the paroxysms of coughing were replaced by attacks of sneezing. The paroxysmal stage persists usually from a month to six weeks, although it may last only two or three weeks; or, in severe cases, much longer. In overcrowded institutions and when the child does not get any fresh air, the paroxysms continue much longer than under more favorable circumstances.

Decline.—The cough loses its paroxysmal character and becomes less frequent. After excitement, emotions, or violent exercise, it may become paroxysmal again for a short time. It may also return after an attack of indigestion or following a heavy meal. For some months any attack of bronchitis is liable to be more or less paroxysmal in character. This stage lasts from one to several weeks.

The Urine.—Gill, Johnston, and others found glycosuria in 16 out of 100 cases. Bendetti claims that the glycogenic function is lowered in pertussis and that very slight excesses of sugar cause glycosuria.

The Blood.—There is a constant leukocytosis, which begins early, before the paroxysmal stage, continues through it, and disappears with it. The leukocyte count varies between 20,000 and 25,000 in the average case, but may run as high as 40,000. All forms are increased, but the principal increase is in the lymphocytes. A blood examination is of great diagnostic value.

The Skin.—In whooping cough, besides purpura, there may occasionally be vesicular or pemphigoid eruptions. Furunculosis is also seen.

Duration.—Epidemics in cities generally last ten or twelve weeks, but they may often persist for six months or even a year. In the largest cities the disease is endemic. The duration of the attack is variously stated, and differs greatly in different epidemics from four to six weeks, from seven to ten weeks, and from sixteen to twenty weeks. Average figures are: incubation one week, catarrhal stage one to two weeks, paroxysmal stage four to six weeks, and decline two to three weeks.

Misuse of Drugs.—This is a frequent cause of symptoms sometimes erroneously attributed to whooping cough. The most frequent are drowsiness, or even unconsciousness, from narcotics; delirium, dry throat, and mydriasis from belladonna; and tinnitus, gastric disturbance, rashes, and other symptoms, from overdosing with quinine.

Other Infectious Diseases.—Measles, scarlet fever, and diphtheria, all of which are unusually virulent in children suffering from whooping cough, are chiefly to be feared (Comby).

Hemorrhage.—This is frequent from the severe coughing spells causing rupture of the swollen vessels. Epistaxis is not infrequent. Ecchymoses into the conjunctiva are frequently seen and of the eyelid may also occur. Conjunctival hemorrhage may cause bloody tears. Small hemorrhages may take place from the ear, either due to rupture of the drum or from the external auditory meatus. Rupture of the tympanum may occur, but, as a rule, causes only temporary inconvenience. Hemorrhage may also take place from ulcerations, nevi, or recent scars, or from the lips, gums, and ulcer of the frenum. Hemoptysis and hema-

temesis are rare. Hemorrhages may be found in the pleura, cerebrum, kidney, adrenals, and other organs at autopsy. Abortion and metrorrhagia are rarely caused by whooping cough.

Respiratory Tract.—Œdema of the glottis has been reported. Spasm of the glottis, the so-called *convulsion interne* of the French, is rare. In this the breathing ceases after expiration, the face swells, the body becomes cyanosed, and the child may fall unconscious and a convulsion follow. The attack ends with a long crowing inspiration and the child breaks out in a profound perspiration. This condition may prove fatal.

Bronchitis is always present during the catarrhal stage, but may be regarded as a complication during the spasmodic stage and defervescence. Congestion of the lungs is not infrequently seen, and is often described as abortive pneumonia. With it fever symptoms like the initial stage of lobar pneumonia, and sometimes even slight dulness, are found; but the condition clears up in a day or two. Bronchopneumonia is the most frequent serious complication and is the cause of nine-tenths of the deaths. It may occur in the very young, in whom it is a particularly fatal complication. Lobar pneumonia is rarer and not so fatal. Pleurisy may be seen occasionally, and an effusion may be present. Bronchiectasis occasionally follows whooping cough, and is said to be frequent after measles and whooping cough together. Acute emphysema is present in nearly every case, and extreme grades may be met with. There may be rupture of the lung and cutaneous emphysema.

Alimentary Tract.—Catarrhal conditions of the stomach and intestine are frequent, and diarrhœa is not uncommon. The so-called mucous disease if present is always aggravated; or, if children have had it, recurrence may be looked for. Prolapse of the rectum may occur, and hernia of any variety may be caused by the severe coughing.

Kidneys.—Albuminuria may be present in some cases. Acute parenchymatous nephritis is a rare complication.

Nervous Complications.—These are numerous and have been studied by various observers. Paul Valentin gives the following classification:

1. Psychoses: (*a*) Delirium, hallucinations; (*b*) depression of spirits (apathy); (*c*) imbecility.

2. Neuroses: (*a*) Hysterical attacks; (*b*) epileptiform attacks; (*c*) choreiform and other convulsive attacks.

3. Motor Troubles: (*a*) Convulsive: *e. g.*, eclampsia, cramps, and spasm of glottis; (*b*) paralytic: *e. g.*, hemiplegia, monoplegia, and aphasia.

4. Sensory Troubles: (*a*) Anesthesia; (*b*) deafness; (*c*) blindness.

Diagnosis.—This is rarely difficult after the disease has thoroughly developed. In the catarrhal stage there is little to separate it from an ordinary bronchitis except the presence of the lymphocytosis. The possibility of infection is also a point of some value, and the occurrence of the disease in the family, school, or friends of the patient should always be sought. A virulent cough in a child who has never had whooping cough is always suspicious, especially if it is prolonged and frequent at night. As soon as the spasmodic stage is reached there is little difficulty. If the child does not have a paroxysm in the presence of the physician one may be brought on for diagnostic purposes by the following

method suggested by Guida: Hold the child as for throat examination; then introduce a spoon along the teeth, and when the child opens the mouth carry the spoon to the base of the tongue in such a manner that the epiglottis comes into view. A paroxysm is produced, and this is more severe in whooping cough than in any of the conditions which may be mistaken for it.

The spasmodic cough from enlarged bronchial or tracheal glands is more like whooping cough than the cough in any other condition. Barthez and Sannée give the following table of differential points:

Whooping Cough	Enlarged Glands
1. Contagious, epidemic.	1. Isolated, not contagious.
2. Three periods, second paroxysmal.	2. No distinct periods.
3. Paroxysmal cough with whoop, vomiting, and viscid expectoration.	3. Paroxysms short, frequent without the whoop, expectoration, or vomiting.
4. Respiratory sounds normal.	4. Signs of enlarged glands sometimes present.
5. Respiration normal in interval; apyrexia if simple.	5. Asthma in some cases alternating with paroxysms. Febrile movements with recrudescence in the evening, sweats, progressive wasting, etc.
6. Voice natural.	6. Sometimes a change in voice.
7. Usually acute.	7. Chronic.

In hysteria there may be a spasmodic cough, but this lasts longer, and there may be bloody expectoration. Croup comes on suddenly and wears off by morning, to recur usually for several nights. Acute œdema of the glottis is attended by inspiratory dyspnœa, aphonia, and shock. Laryngismus stridulus has no prodromes, is often accompanied by carpopedal spasms, and the course is different. Spasmodic cough may occur in catarrhal laryngitis, with elongated uvula, adenoids, and enlarged tonsils. Paroxysms of coughing not unlike whooping cough may be caused by foreign bodies, such as feathers, pebbles, etc., in the larynx, trachea, or bronchi. The coughing ceases when the foreign body is dislodged. Ictus laryngicus, or the so-called laryngeal vertigo, is attended with a spasmodic cough. There is a burning sensation in the larynx, cyanosis, and the patient falls to the ground. The arms and legs are relaxed or twitch convulsively. Recovery is rapid.

Prognosis.—According to the older writers whooping cough was a very fatal disease. In England the mortality is still rather high. In America the disease is regarded as a mild affection, notwithstanding that in 1900 there were 9958 deaths from whooping cough, a higher mortality than from scarlet fever. The older the child the more favorable is the prognosis. In nurslings and children under three years of age the outlook is serious. The causes of death are pneumonia, inanition due to loss of sleep and constant vomiting, hemorrhage into the brain, external hemorrhage, asphyxia, syncope, convulsions, and bronchitis. Death has resulted from secondary nephritis. In overcrowded institutions the disease is prolonged and fatal, and this is also true wherever there is overcrowding and lack of fresh air.

Prophylaxis.—The child should be isolated and the room disinfected if it is to be occupied by a young child. Special care should be taken to avoid infecting young children and those with other diseases. There

are no measures which will prevent an individual taking the disease, if he is susceptible, except the avoidance of infection. The patient should be regarded as a source of infection until the spasmodic stage is over.

Treatment.—Much can be done to make the course of the disease less severe, but it is extremely doubtful if any treatment has an influence in shortening the duration. Hygienic measures are of great importance. The child should lead a quiet, outdoor life, free from all excitement. The more the child is in the fresh air the less severe the disease. The sleeping apartments should be thoroughly aired during the day and well ventilated at night. If the child cannot be outdoors, he should be taken from room to room and not allowed to spend all the time in one unaired room. The temperature should be even and the child protected from extremes and also from winds, dust, and irritating vapors. The clothing should be suited to the weather and the child clothed with sufficient warmth, but not burdened with extra wraps either by day or night. In cold weather the bed should be warmed before the child is put into it, as contact with cold sheets is liable to bring on a paroxysm.

The diet should be light and nourishing. Younger children may be put on an exclusive milk diet, and this should also be done whenever there is much vomiting. The feeding may become a serious problem, and it should be the first care from the onset. If one meal is vomited, another should be given immediately, as each paroxysm is usually followed by a period of comparative quiet. In such cases the amount given should not be too large. Rectal enemata may be used if necessary. Great care should be taken not to upset the stomach by drugs.

Psychic treatment is of some value, and the child should be instructed to cough as few times as possible. Most of the paroxysms come on spontaneously, but some nervous children do an unnecessary amount of coughing. Strong emotions may bring on or cut short paroxysms, and the number may be diminished by fright.

Anything which reduces the number of paroxysms or cuts them short is of great value, as it lessens the danger from prolonged and severe coughing. Nägeli has suggested an ingenious method of stopping the paroxysms. This consists in pulling the jaw forward and downward in the manner frequently employed by anesthetists. This can be done by the mother or nurse every time the child feels a paroxysm coming on. Kilmer recommends a snugly fitting elastic band about the abdomen applied as follows: A stockinette band, similar to those used under plaster jackets, is applied to the body from the axillæ to the pubes, and two shoulder straps are used to keep it from slipping. On this stockinette a width of silk elastic is sewed so that it goes around the body and covers the entire abdomen. It should be pinned slightly on the stretch and then sewed on so as to keep it from curling.

The idea that vaccination influences the course of whooping cough dates from Jenner's time. Poschi advises vaccination at the beginning of an epidemic. He states that it has no curative effect after the disease has passed the initial stage, but has when it is practised during incubation. Recent vaccination protected those who had been recently exposed, but children vaccinated a year previously were not protected.

Inhalations, sprays, and insufflations of powders have been recommended. Among the best inhalations are creosote, oil of eucalyptus, and carbolic acid vapors. A dram (4 gm.) of any one of these is added to a pint (500 cc.) of water and the steam inhaled. Sulphurous acid obtained by burning sulphur pastilles is also used. Bravo and Soltman use cypress oil. This is diluted with alcohol 1 to 5, and from 2 to 3 drams (8 to 12 cc.) are poured on the pillow or underclothing four times a day. Of the sprays, 2 per cent. solutions of salicylic acid or resorcin are the most highly lauded. The throat is sprayed every two or three hours, the child being told to breathe deeply while it is being done. Local applications of various kinds are made to the nose and throat.

Internal Medication.—No one drug acts equally well in all cases and the effect of any drug may diminish if used continuously, but after stopping it for some time it may be resumed with benefit. Any medication causing nausea or vomiting should be stopped immediately. The following are the most useful of the numerous drugs recommended: Heroin hydrochloride is one of the very best, as it quiets the cough and exerts a sedative action. It is best given in an elixir in doses of gr. $\frac{1}{1000}$ to $\frac{1}{240}$ (0.00065 to 0.0027 gm.) four to six times a day. Belladonna is given as the tincture, in doses of from 1 to 10 minims (0.06 to 0.6 cc.) four or five times a day. A small dose should be given at first and this increased until slight flushing is observed about twenty minutes after it is administered. This dose may be continued. Blonds require much smaller doses than brunettes. Antipyrine is a most valuable drug. It should not be given too continuously nor when the heart is weak. It may be given in doses of 1 to 5 grains (0.0625 to 0.324 gm.). Codeine sulphate may be added to this with advantage. From gr. $\frac{1}{60}$ to $\frac{1}{4}$ grain (0.001 to 0.016 gm.) may be used, according to the age of the child. For younger children it is best given in syrup of orange; older children may take it in capsules.

Quinine, as suggested by Binz, is of considerable value, especially in older children; but the large doses in younger children are liable to cause nausea. It is given in doses of about gr. $\frac{1}{6}$ (0.01 gm.) for each month of the child's age, and about gr. $1\frac{1}{2}$ (0.1 gm.) for each year of the age. This dose should be given four times a day. Camphor has many advocates. Croton chloral hydrate is advised by Eustace Smith. He gives 1 grain (0.06 gm.) every two, three, or more hours, according to the age of the child and requirements. It is often useful to add to this a double quantity of potassium bromide. Bromoform is of great value in lessening the number and severity of the paroxysms, but there is danger of poisonous effects from overdosage. It should not be prescribed among ignorant or careless people. From 1 to 5 drops may be given at a dose, best on sugar. Emulsions should be thoroughly shaken before each dose. Excessive vomiting can sometimes be relieved by cocaine given twice daily. About gr. $\frac{1}{6}$ (0.01 gm.) is given at a dose.

A vaccine has been prepared from the Bordet and Gengou organism, but so far the results have not been very satisfactory. Several curative serums have been tried without results.

CHAPTER XVI

UNDULANT FEVER

By COL. SIR DAVID BRUCE, C.B., F.R.S., D.Sc., F.R.C.P.

REVISED BY

GEORGE C. LOW, M.A., M.D., C.M.

Synonyms.—Mediterranean or Malta fever.

Definition.—A disease of long duration, characterized clinically by continued fever, profuse perspiration, constipation, frequent relapses, rheumatic or neuralgic pains, swelling of joints, or orchitis; bacteriologically, by the presence in the blood and organs of the *Micrococcus melitensis* (Bruce); and, anatomically, by congestion of the spleen and other organs.

Geographical Distribution.—Undulant fever has been reported from *Spain*—Gibraltar; *Islands of the Mediterranean*—Balearic Islands, Corsica, Sardinia, Sicily, Malta, Gozo, Cyprus, Crete; *Italy; Greece*—Athens; *Turkey*—Constantinople, Smyrna; *Palestine*—Jerusalem; *Africa*—Tunis, Algiers, Alexandria, Suakin, Massowah, Zanzibar, Kimberley, Orange River Colony, Uganda and Northern Nigeria; *Arabia*—Aden; *India; China*—Hong Kong; *Pacific*—Philippine Islands, Fiji Islands; *North America*—Mississippi Valley, Texas; *West Indies*—Cuba, Porto Rico; *South America*—Venezuela, Brazil, Montevideo. It is probable that many of these reported cases were not really undulant fever, the diagnosis often depending on the serum reaction alone. The distribution of the disease is widespread, however, and may be described as tropical and subtropical, no cases, according to Hughes, having been reported north of 45° N. latitude, or south of 40° S. latitude.

Distribution in Malta.—Undulant fever was thought at one time to be chiefly confined to the large towns of Malta, but it is now known to occur in every part of the island, and the disease is prevalent in several of the inland towns and villages. The average incidence of the fever among the 200,000 Maltese used to be about 30 per 10,000; while among the soldiers quartered in the island it was about 370 per 10,000. Within recent years, owing to the discovery of the cause of its spread, the disease has disappeared from the army and navy.

Etiology.—The Micrococcus Melitensis.—This coccus, or coccobacillus, is about 0.33μ in diameter, and usually occurs singly or in pairs, but when grown in broth appears in short chains. A bacillary form also occurs in cultures which have been grown at ordinary temperatures (18° to 20° C.). It is non-motile. It stains readily with all the basic aniline dyes, but loses its color rapidly when treated with alcohol or other decolorizing agent; it is Gram negative.

Artificial Cultivation.—Growth is extremely slow; faintly acid media should be used. If markedly alkaline no growth takes place. Slow and scanty growth takes place at a temperature of 18° C., but the optimum temperature is about 37° or 38° C. At temperatures between 40° and 42° C. growth is suspended. Above 42° C. artificial growths die. It is aërobic, but also grows in a feeble way anaërobically. The chief cultural characteristics are as follows: It grows in glucose peptone (1 per cent.), in lactose, saccharose and starch peptone without producing acid or gas. In litmus milk there is no clotting, and the reaction becomes distinctly alkaline in a few weeks. On potato it grows well; the growth is moist, transparent, and the formation of chains is well-marked. *Broth.*—After two or three days the broth becomes turbid. If allowed to stand for some time there is a deposit of flocculi, but the fluid remains turbid, and there is no pellicle formation. Indol reaction is negative. No odor is produced. *Gelatin.*—No liquefaction. *Agar-agar.*—Cultures made directly from the organs after death on this medium, if faintly alkaline, show no growth for about four days if kept at 37° C., and seven days if kept at 25° C. On sloped agar the colonies when they do appear are small and transparent, and resemble drops of dew.

Plate Cultivation.—On ordinary agar at 37° C., after three days, under the microscope the colonies on the surface are round, with an even border. They are bright and transparent, with a slight brown tinge about the centre, and are finely granular. As they grow older they become browner in color.

The addition of 1 per cent. nutrose enhances and quickens the growth of the micrococcus. To separate it from a mixture of others, it is best to use a medium to which glucose, nutrose, and litmus are added. The fact that it does not ferment glucose, and renders milk and other media alkaline, is an important feature, while the addition of nutrose adds somewhat to its rate of growth. On such a glucose-nutrose-litmus agar, the colonies appear blue, whereas many of the streptococci found in urine, feces, etc., ferment glucose and give the medium an acid reaction.

In regard to the diagnosis of this species of bacteria, Horrocks says that a microörganism which agglutinates with a specific animal serum in a high dilution, does not ferment glucose, renders milk alkaline without coagulation, and does not retain the stain by Gram's method, may justly be regarded as the *M. melitensis.*

Micrococcus Para-melitensis.—Recently, Nègre and Raymond[1] have demonstrated a variety of the *M. melitensis* which they propose to call *M. para-melitensis.* The organism was obtained from Nicolle in Tunis. It differs in its agglutination reactions. Bassett-Smith[2] describes a case of this para-melitensis fever, in which the blood serum agglutinated the *M. para-melitensis* but not the ordinary *M. melitensis.* The clinical features of the disease were the same as ordinary undulant fever.

Life of the Micrococcus Melitensis Outside the Body.—*Vitality.*—The germ is fairly resistant when outside the body; it resists desiccation in

[1] *Compt. rend. Soc. de biol.*, May 24, July 5, 1912.
[2] *Jour. Trop. Med. and Hyg.*, February 15, 1913.

dust or on dry fabrics for sixty or eighty days, and will live in tap- or sea-water for about a month. Even in urine which has become markedly alkaline it has been found alive after six days. Exposure to the sun kills it in a few hours.

Habitat Outside the Human Body.—The parasite has, so far, not been found in external nature. On account of the high temperature required for its growth, the length of time which elapses before the colonies appear, and the absence of any well-marked morphological or cultural characteristics, the search for it outside the body will be very difficult, if not hopeless. Many efforts have been made to find it in the air of wards, in dust from infected rooms, in the water of the harbors, or in the soil. Examinations of these materials have been made without result.

The Paths by which the Micrococcus Leaves the Body.—The urine frequently contains them, sometimes in enormous numbers, but, as a rule, they are not numerous, ranging from 3 or 4 to 300 or 400 per cc. Kennedy reported that he made some three thousand observations. on the urine and found the *M. melitensis* in 10 per cent. This, taken in connection with the long-continued vitality and virulence of the organism in a dry condition, may be a factor in the spread of the disease, though it must be confessed that up to the present there is no direct proof of infection by naturally infected dust. This excretion in the urine may go on for a long time (two years) after the patient is convalescent, so that these microbes must be scattered broadcast. It has not yet been ascertained how many cases remain unidentified, but there can be little doubt that many do, and these add to the general contamination of the surface of the soil. Shaw[1] examined 525 dockyard laborers and found that 79, or 15 per cent., gave a distinct agglutination with the *M. melitensis*. Of these 79, a marked reaction was present in 22, who were accordingly selected for a detailed examination. In 3 of them the organism was recovered from both blood and urine, in 1 from the blood only, and in 6 from the urine only. All these men were at work during the period of observation. Two were kept under observation and continued to pass large numbers of micrococci in the urine from June, 1905, until the end of 1906, and are probably still excreting them.

Although the micrococci have only been directly observed in the feces of man on one occasion, they probably also pass out of the body by way of the alimentary canal. Eyre found micrococci throughout the whole length of the intestine in artificially inoculated rabbits. Horrocks and Kennedy have also found them in the gall-bladder of man.

A third way of leaving the body is by the milk, and this is by far the most important from the point of view of infection. Naturally, it is difficult to obtain evidence of this mode of excretion in human patients, on account of the absence of lactation in those who have undulant fever. During the summer of 1906, however, 3 women were examined and the micrococcus recovered from the milk of 2 of them.

These three modes of leaving the body are probably the most important. The possibility of biting insects, mosquitoes or otherwise, extracting

[1] *Reports of the Mediterranean Fever Commission*, vol. iv, p. 8.

cocci from the blood has also to be borne in mind. Although this has not been disproved it can only be of very rare occurrence.

The Paths by Which the Micrococcus Enters the Body.—The success of preventive measures depends on this. Does the virus enter by the alimentary canal, by the lungs, through mucous membranes, or through the skin? Is it conveyed from the sick to the healthy by means of food, water, milk, by the inhalation of dust, or is it injected through the skin by suctorial insects? The work of the Mediterranean Fever Commission has clearly shown that in nature the ingestion of infected goats' milk is the usual means by which the disease is spread. Other methods play only a very minor part.

By Contact.—Many experiments have been made on this point, as naturally, questions of segregation of the sick, evacuation, and disinfection of infected barracks and rooms depend on this mode of infection. In 1904 two monkeys belonging to the Mediterranean Fever Commission took the fever naturally. They were both living close to affected monkeys, and it was supposed, and probably rightly so, that they had taken the disease from their neighbors. This was repeated as an experiment on several occasions with, as a rule, positive results. Experiments made in which the contact was limited, that is to say, in which infection by urine was excluded, never succeeded. It was therefore concluded that the monkeys probably took the disease by having their food contaminated by the urine of their neighbors; and that, therefore, contact resolved itself into a feeding experiment.

As the chance of man having his food contaminated in this way is very remote, it is probable that few cases arise in this manner.

By Contaminated Dust.—As the organism can retain its vitality for a long time in a dry condition, it was thought probable that the infection might be conveyed from the sick to the healthy by means of dust. Dust contaminated with infected urine might be blown into the atmosphere and so be inhaled or swallowed. A series of experiments was made to prove or disprove this, and from these it may be concluded that *artificially* contaminated dust may convey undulant fever to healthy animals. This is not proof, however, that this ever occurs naturally, as dust in nature can contain but few micrococci, seeing how sparse they are in the urine, as a rule. The dust blowing about under natural conditions must rapidly dilute the micrococci to an extraordinary extent, so that one can only picture a micrococcus here and there in a great quantity of dust. The natural conditions can be more closely imitated if the dust is contaminated with infected urine and not from a culture.

By Dust Artificially Contaminated by the Urine of Undulant Fever Patients.—A urine containing micrococci was used to contaminate the dust. After drying, the infective dust was blown into the nostrils and added to the food of monkeys. Four experiments are reported by Horrocks, lasting from twelve days to two months; no infection occurred. It is difficult to understand why this experiment did not succeed. The dust was infected by a urine containing exceptionally large numbers of the micrococci, and immediately dried. It was evidently added in fairly large quantities to the food, as three out of four animals suffered from

severe vomiting and diarrhœa. Shaw also experimented on four monkeys in the same way, but failed to convey the infection in a single case. These experiments are much more severe than anything we can imagine occurring in nature, and tend to throw doubt on dust being an important factor in the spread of the fever.

By Dust Collected from Suspicious Places.—This is, of course, the crucial experiment so far as infection by dust is concerned. Judging from the non-success of the last series of experiments with urine-contaminated dust, it was not likely that this experiment would succeed. Dust was collected from fever wards, from places where cases had occurred, from around urinals, etc., and blown about the cages and food of monkeys, or injected subcutaneously. Up to the present all these experiments have failed.

By Way of the Alimentary Canal.—It has been repeatedly demonstrated by experiment that a small quantity of a culture applied to a scratch, or injected under the skin, will give rise to undulant fever in man and monkeys. Also that dust or fluids containing the micrococci, if applied to the unbroken conjunctiva, nasal passages, pharynx, interior of the larynx and trachea of monkeys, will set up this fever.

This question of the micrococcus gaining entrance by way of the alimentary canal is important, and many experiments were made by the Commission to settle this point. The result of these proved that animals can be readily infected by contaminated food or drink. For example, a single drink of milk containing comparatively few micrococci almost certainly gave rise to the fever.

Infection by Means of Goats' Milk.—Attention was directed by the Commission to the goats, which supply most of the milk used in Malta. Healthy goats were injected subcutaneously with cultures of *M. melitensis*, and, although they showed no signs of fever or ill-health, an examination of their blood demonstrated that the micrococci were living and growing. This led to the examination of various herds of apparently healthy goats supplying the inhabitants with milk, and the important discovery was made that about 50 per cent. were affected by the disease, and that 10 per cent. were actually excreting the micrococcus in their milk. Monkeys fed on milk from an affected goat, even for one day, almost invariably took the disease. At this time, curiously enough, an important experiment on the drinking of goats' milk by man occurred accidentally. This was the case of the S. S. "Joshua Nicholson." In 1905 this steamer shipped sixty-five goats at Malta for export to the United States of America. The milk was drunk by the captain and many of the crew, with the result that an epidemic of undulant fever broke out on board the vessel, almost everyone who drank the milk becoming infected. Even after the goats reached America and were placed in quarantine, a woman who drank some of their milk also got the fever.

This infection of goats explained many of the curious features in the epidemiology of undulant fever: The irregular seasonal prevalence and the number of cases during the winter months, when there are no mosquitoes and little dust. It is true there are more cases in summer,

but this may be explained by the conditions being more favorable for the multiplication of the micrococcus, by more milk or cream being used for fruit, in ice-cream, etc., and by the lowering of health during the hot months. It explained the large number of cases arising among patients in hospitals where milk is used largely, also the liability to attack of the officer being three times as great as the private soldier, since the former consumes much more milk than the latter. It also explained the isolated epidemics which sometimes occur in institutions.

Result of Preventive Measures Directed against the Use of Goats' Milk.—These were first begun in Malta in June, 1906, and the result was very striking. In July, August, and September, 1905, there had been 258 cases among the soldiers, whereas in the same months in 1906 the number fell to 26. Another striking example of the benefit of this simple preventive measure is given in the case of the Naval Hospital, Malta. This is a fine modern building, situated in extensive grounds. In spite of these advantages many cases of the disease had occurred among its inmates, almost every patient who remained for a few weeks in the hospital becoming infected. The goats supplying the hospital were examined and several were found to be passing the micrococcus in their milk. The use of this milk was forbidden, and from that date not a single case of undulant fever has appeared in the hospital. In Gibraltar, where some years ago this fever was prevalent, it has disappeared *pari passu* with the disappearance of Maltese goats. Nine-tenths of the cases of undulant fever occurring in Malta have now been shown to be due to goats' milk, and this discovery has saved the army and navy seventy-four thousand eight hundred and eighty days of severe illness yearly. This brilliant achievement demonstrates the value of experimental methods in the elucidation of the etiology of disease.

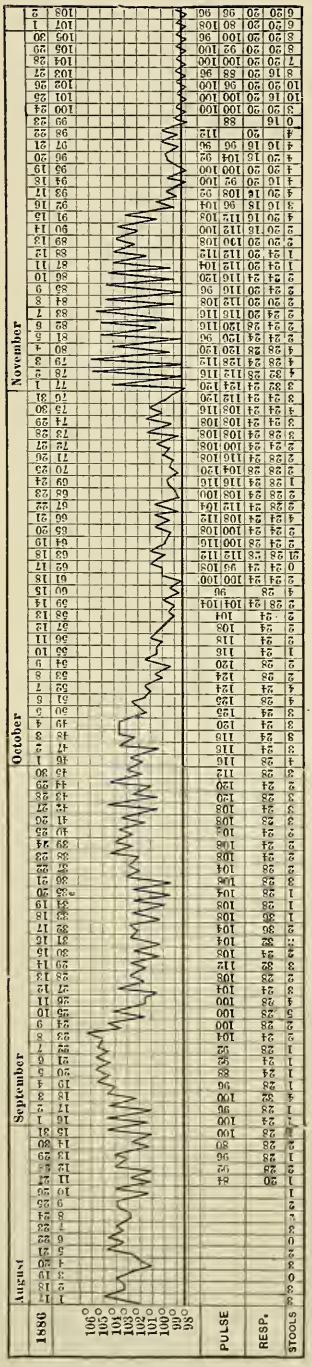
Age and Sex.—There are no statistics available at the present time to enable us to state whether age or sex has any bearing on the incidence. In former papers by the writer, the opinion was hazarded that any age is liable and that sex has no influence.

Incubation Period.—It is impossible to state exactly what this is. Johnstone provisionally states that the available data tend to suggest that the incubation period is about fourteen days. One case is reported by Bassett-Smith with an incubation period of two months, but it stands alone, and there is some evidence that cases have occurred in as short a time as six days after arrival in Malta. The subcutaneous inoculation of monkeys gives an incubation period of about five days, whereas if the disease is given by ingestion the inoculation period appears to be lengthened to about fifteen days.

Immunity.—Although there is some diversity of opinion, the writer's experience suggests that one attack of this fever practically confers immunity. Several monkeys which had recovered from the disease were reinoculated with virulent cultures but showed no reaction.

Special Pathology.—The anatomical changes are those due to high temperature and the circulation of toxins in the blood, and need not be described in detail. There is no specific inflammation of Peyer's patches, or other glands of the intestine. The spleen is always enlarged, averaging

Fig. 12



twenty ounces in weight. The mesenteric glands are only moderately enlarged. The lungs are always congested at the bases, but there is less liability to pneumonic consolidation than in typhoid fever.

Symptoms. — The symptoms are those commonly met with in other fevers, such as typhoid fever. There are, however, a few points which should be noted. For example, constipation is a marked symptom; in 65 cases, 48 are noted as being constipated throughout, whereas only 17 had diarrhœa at any time during the illness. The temperature curve must also be noted. On looking over a series of charts, the striking features are the extreme irregularity and the great tendency to relapses. The following chart may be taken as typical of a fairly severe attack and from it can be judged the length and serious nature of the disease.

Duration of the Fever.—The average stay of soldiers in hospital is ninety days, but this does not represent the true average, as many of these men are invalided to England. Bassett-Smith gives the average duration in 50 cases at one hundred and twenty days. The length of this fever varies in different individuals between wide limits, while some return to duty within twenty or thirty days; on the other hand, the writer has seen a case which lasted for more than three years.

Another important symptom is the pain and swelling of the joints. This complication occurs in nearly half the cases, and is very characteristic. Neuritis and orchitis come under the same category, and are fairly frequent. The orchitis is painful while it lasts, but usually passes away in a few days without leaving any bad effects.

Sequelæ. — There is little to be noted under this heading. Although considerable pain and inconvenience are caused by the swelling of, and effusion into, the joints, the arthritis usually clears completely and does no permanent damage. Neuritis is frequent in various nerves, and tends to cause, in a few cases, prolonged anesthesia, paresis, or

even paralysis, of various regions and groups of muscles. In time these return to normal, and complete recovery follows.

Mortality.—The disease is not a very fatal one, 3 per cent. being the case mortality in the army during a period of seven years.

Diagnosis.—This is most important clinically in the distinction from typhoid fever, from which it differs chiefly in the longer duration, in the absence of rose spots, in constipation being the rule, and in the frequent occurrence of painful arthritic or neuralgic symptoms. The surest method of diagnosis is the finding of the *M. melitensis* in the blood, *intra vitam*, or growing it from the spleen *postmortem*.

If a diagnosis cannot be made in this way there remains the agglutination test. To trust to this alone is dangerous, however, and every examination should be safeguarded by control experiments. The *M. melitensis* will give a positive agglutination reaction with almost all specimens of serum in dilutions of 1 in 2 and blood taken from cases other than undulant fever will sometimes show signs of agglutination at 1 in 10, though this is the exception. A complete sedimentation is never obtained at 1 in 20 unless the blood is from a patient with undulant fever. The agglutinins may persist in the blood for long periods. It is reported that about 50 per cent. of patients will show the agglutination phenomenon two years after the illness in dilutions of 1 in 10, and one instance is reported as giving a positive reaction in a dilution of 1 in 20, seven years after recovery. This source of error must be kept in mind.

One quality about the serum from patients with the disease is that if it does agglutinate the micrococci it does this in no uncertain way. The average dilution giving a complete reaction is given as 1 in 500, and cases have been reported up to 1 in 6000. The time which elapses from the commencement of the fever to the appearance of agglutinins in the blood is usually put down as five days. As to the lowest dilution which may be accepted as proof of undulant fever, some workers put it at 1 in 10, if the clumping is well-marked and takes place at once or within half an hour. In the writer's opinion 1 in 20 is a safer dilution.

Prognosis.—This is very favorable as regards life and ultimate recovery. If the patient tides over the first two or three weeks, he usually recovers. Death occurs, as a rule, in the first week or two of the disease, and is preceded by continued high temperature with a tendency to hyperpyrexia, delirium, dry tongue, and diarrhœa. A patient sometimes dies at a later stage, but this is rare.

Treatment.—The essential points in prophylaxis are evident from the discussion of the etiology. Every care should be taken to exclude all articles of food from the diet which may contain the causal organism.

In the treatment there is no specific drug and the majority of patients are best treated without medicines. Quinine and salicylic acid are useless. Symptoms must be treated on ordinary principles as they arise. The tendency to hyperpyrexia in severe attacks is one of the most important symptoms. Hydrotherapy is the most useful measure, sponges or baths being given. Sleeplessness, headache, arthritis and orchitis must be treated on ordinary principles. Vaccine treatment has not given any special results.

CHAPTER XVII

ASIATIC CHOLERA

By W. P. DUNBAR, M.D.

Epidemiology and Etiology.—The oldest known description of cholera seems to be that of the Hindu Sucruta. In this the following symptoms are emphasized: diarrhœa, vomiting, thirst, stabbing pain, and coma. *Cholera Asiatica* occurs in the form of epidemics which, following the paths of human traffic, spread quickly over wide areas and carry off 50 to 55 per cent. of those affected. No disease showing these features, and at the same time presenting a definite tendency to epidemic distribution, appeared in the civilized world, certainly not in Europe and America, before the beginning of the nineteenth century. Since then it has repeatedly encircled the earth; scarcely a country has escaped. Only such regions as are reached from India by a long sea trip, such as Australia and Cape Colony and the unfrequented regions of the Arctic Zone, high mountainous districts, etc., remained free. The origin of epidemics has always been India, where its real home is, and more precisely in the lowlands of the southern parts of Bengal with Calcutta for the chief city.

The question is of great interest, whether by modern methods of combating the disease it will be possible to limit it or whether we must reckon with its further wandering in the accustomed way. In 1905 the disease was introduced into Germany from Russia, 100 workers on river boats having cholera, but there was a total of only 254 cases in Germany, no place having more than 2 or 3 cases. In 1906 no cases occurred in Germany, which shows the benefit of energetic measures against the disease. It is generally agreed that cholera, following always the principal paths of human intercourse, has spread from point to point with greater rapidity as the rate of transport has increased. It has followed the course of shipping as well as that of traffic by land. With changes in the paths of traffic the route of cholera changed also.

The cholera expedition sent to Egypt in 1883, under Koch, found in Alexandria an opportunity to study 11 living cholera patients, and the cadavers of 10, a few hours after death. The investigation of the intestine showed in all cases (with the exception of 1 which ended fatally as the result of a secondary disease several weeks after the recovery from cholera) the presence of a definite organism. On Koch's suggestion the expedition was sent to India to continue investigations there and they succeeded in making pure cultures of the organism. The investigation of 42 cholera cadavers and 28 cholera patients resulted without exception in the confirmation of the findings which had been reached in Egypt. It was always possible, both from all cholera corpses as well as

from the dejecta of the cholera patients, to isolate a quite characteristic comma-shaped bacterium, a vibrio.

In spite of the force and clearness of Koch's proofs, there were, not only among the laity but even among physicians, very numerous adherents of the localistic theory. The fact that this theory rejected all quarantine, isolation, expensive disinfection, etc., in the combating of the disease made this doctrine especially popular and gained a ready hearing in circles which were interested in commerce. When, in the year 1892, the cholera appeared in Hamburg suddenly and without warning and in a few weeks, out of a population of about 600,000, attacked almost 17,000 and carried off 8600, the whole civilized world was aroused and naturally all possible means were used to arrive at a definite solution as to its cause and mode of spread. From Hamburg cholera was transported to 268 other places. The government sent trained men to these places, who, basing their ideas on Koch's theory, ordered the necessary precautions. In all these places together, excepting Hamburg, not more than 800 persons succumbed. In the year 1893 there were again 114 different places in Germany visited by cholera, but in all only about 300 persons died. Although Germany was especially threatened from Galicia and Russia, the pestilence did not succeed in gaining a foothold because suspected individuals were carefully guarded and special care was taken that no water suspected of infection was used. In the year 1894 the cholera gained entrance again into 157 towns of Germany, but only 490 persons in all died of the disease. In the year 1895 no cholera appeared in Germany. The epidemic thus ended in three years, while earlier epidemics had lasted an average of ten years.

Everywhere the cholera appeared, the organism described by Koch was found. His theory was thus most brilliantly confirmed. According to it the infectious agent occurs in the dejecta of the cholera patients, and is usually transferred to others by objects which become infected. Especially important is polluted water. According to Koch transportation by the air never occurs.

The Cholera Vibrio.—Morphology and Cultural Characteristics.—The bacteria are about 1 to 1.5μ long and 0.3 to 0.5μ thick. They are not quite straight but slightly curved like a comma, and this curvature may be so great that the rod takes the form of a semicircle. In pure cultures these rods often form S-shaped figures and longer and shorter wavy lines, of which the first represents two individuals and the latter a larger number of cholera bacteria which have remained connected after a continued multiplication. They possess independent motility which may be best observed in a hanging drop. The size and form vary somewhat. In some cultures they show a length of 1μ while in others they are about 3μ. Certain strains show quite short curves with very little twisting, while others are very much twisted. The cholera vibrio takes up basic aniline dyes well. It is completely decolorized by Gram's solution. It is generally recommended to stain with diluted Ziehl's fuchsin solution (1 to 9).

Especially characteristic is their behavior in nutrient gelatin, in which they form colorless colonies which, with low magnification, resemble,

after twenty-four hours, bubbles which are not quite circular but show an irregularly partly scalloped contour. Very soon they assume a somewhat granular appearance, which comes out more sharply in the large colonies, until the latter seem as if composed of highly refractive granules. With further growth the gelatin liquefies in the immediate neighborhood of the colony and the latter sinks somewhat deeper into the gelatin. It forms in this way a small funnel-shaped depression, in the middle of which the colony is visible to the naked eye as a whitish point. The liquefaction of the gelatin never extends very far in the neighborhood of the colony (provided that the colony is isolated enough), a property which distinguishes the colonies of cholera bacilli from many others. The macroscopic appearance of a gelatin plate, which contains numerous young colonies lying close together, is also characteristic. The surface of the gelatin resembles a ground-glass plate.

Gelatin and Agar Cultures.—For years gelatin plates have been almost exclusively used in the isolation of cholera vibrios, but investigations have shown that the growth does not always occur on gelatin plates in the typical way, but that considerable variations may occur. Nevertheless these do not make the gelatin plate deceptive for diagnostic purposes, and even the most atypical cholera colonies are easily distinguished from the intestinal bacteria which are commonly found. Various mixtures of agar and gelatin have been proposed which might allow the characteristic growth of gelatin plates together with the possibility of a more rapid cultivation. It has, however, proved simpler and just as effective to use ordinary agar plates. The use of agar to which 10 per cent. of blood is added is of value.

The colonies of cholera bacilli developing on the surface of the agar are brighter and more transparent in reflected light than the colonies of ordinary intestinal bacteria. One frequently observes in the colonies of cholera organisms a margin, or ring formation, but the growth of these colonies is not so characteristic as on the gelatin plates. It is, therefore, advisable to transplant several of the suspicious colonies for further investigation. Although the result can be reached more quickly with agar than with gelatin plates, one should nevertheless inoculate the latter at the same time. There are cases in which the gelatin plates lead more surely to the desired result. This is especially true of the investigation of suspected drinking water.

Methods for Accelerating the Growth.—With the appearance of a disease suspected of being cholera, it is important to make a diagnosis as quickly as possible and efforts were made to discover conditions more favorable for the increase of the cholera than for other bacteria. Schottelius pointed out, in 1885, that the cholera vibrio is highly dependent on oxygen, and therefore accumulates rapidly at the surface of fluid cultures. If, therefore, cholera dejecta are covered with bouillon and put in a warm place, the cholera vibrios can be found in masses on the surface of the culture after ten or twelve hours. In the Hamburg epidemic of 1892 the writer observed that the cholera vibrio found particularly favorable conditions for growth in peptone solution which was inoculated with the cholera dejecta for the purpose of developing the

cholera red reaction, and soon collected on the surface in the form of a scum, as described by Schottelius. The writer repeatedly succeeded, in cases where plate cultures failed, in cultivating the vibrios by inoculating gelatin or agar plates from a solution of peptone which had been inoculated with dejecta and kept for three, six, or nine hours at 37° C. The writer succeeded in a number of cases in obtaining the bacteria from suspected water. Koch at once took an active interest in this method, but he has never claimed to be its discoverer. Nevertheless, it is given his name by some writers.

An especial advantage is the fact that larger masses of infectious material can be investigated, *e. g.*, several cubic centimeters of feces. Repeatedly the writer succeeded in demonstrating the cholera vibrio in material in which the direct agar or gelatin cultures were unsuccessful. Of the suspected water even greater quantities were used than in the case of dejecta.

Cholera Vibrios in Healthy Persons.—Koch held the view that, in Europe at any rate, man must be regarded as the real bearer and reproducer of the cholera organism. Many isolated epidemics could theoretically be explained only on the assumption that completely healthy persons, or persons not noticeably diseased, had introduced the organisms. This was first confirmed by the winter epidemic in Hamburg in 1892–93, when the writer with the help of the peptone culture medium was able to recognize the cholera vibrio in no less than 28 persons who were completely healthy and had never suffered any symptoms of cholera or the slightest diarrhœa. The importance of this discovery was misconstrued by many and used as the starting-point for attacks on the Koch cholera theory.

The Length of the Stay of the Cholera Vibrio in the Intestine of the Diseased.—As a rule, living bacteria are not found longer than eight or ten days. Rommelaire found them after forty-seven days and Kolle after forty-eight days. According to this, it must be regarded as definitely established that apparently quite healthy persons may carry around for a month and a half the cholera organism in a condition capable of developing, and in that way give rise to further infection.

Duration of Life of the Cholera Vibrio in Dejecta.—Investigations have, as a rule, indicated that the cholera vibrio can live only two or three weeks in dejecta. But the writer was able to demonstrate cholera vibrios, still capable of developing, in cholera dejecta, kept at room temperature or on ice, after one hundred and sixty-three days.

Influence of Temperature.—The vital power of the cholera vibrio is far greater at medium and low than at high temperatures. Formerly it was believed that it, as a native of the south, demanded a high temperature and that it must perish at a low temperature. Therefore it was incomprehensible how the cholera could winter among us, but the writer has preserved cholera dejecta at a temperature of about 0° C., and still found vibrios capable of developing after twenty days. It has been possible to cool the cultures to —31.8° C. without destroying the organism. Even when the cultures were alternately frozen and

thawed twelve times they still contained living vibrios. Kansasky kept cholera cultures four months at a temperature between —6° and —31.8° C. without the destruction of the vibrios.

Behavior of Cholera Vibrios in Corpses and in the Ground.—The vibrios perish very rapidly in the bodies of those dead from cholera. The writer made extended investigations in this direction but they were all negative. They are of special interest on account of the fact that the land in which the cholera corpses were buried was drained to the depth of from 1 to 1½ meters. We investigated the drainage water and found this not only free from cholera vibrios but also almost free from any living bacteria, although the rain water passed through the ground in which thousands of cholera corpses had been buried. In buried guinea-pigs which had died of cholera infection, Petri, von Esmarch, and Klein were able to demonstrate the cholera vibrios only up to the fifteenth and nineteenth days.

Power of Development of the Cholera Vibrio in Water.—What becomes of cholera vibrios when they pass into water? Until recently the view was held by many that the cholera vibrio which passed into water rich in other bacteria must be destroyed within a very short time, and that there could hardly be any question of their increase under such conditions. This is a problem of great interest. If we must reach the conclusion that the cholera vibrios possess far greater powers of resistance in presence of other water bacteria or even the power of increasing in impure water, many still unsolved epidemiological problems would receive a satisfactory explanation. In the writer's opinion the material already before us is sufficient to prove that, even in our climate, the cholera vibrio is able not only to persist a long time in spring and river water, but that under certain conditions it can even increase.

The cholera vibrio does disappear rapidly in certain water, *e. g.*, according to Hankin, in the Ganges and Jumna Rivers, but it seems to find in the water of the Elbe very favorable conditions for development. After the epidemic of 1892, many kinds of vibrios, whose biological characters were extraordinarily similar to those of the cholera vibrio, appeared yearly for some years in enormous numbers in the water of the Elbe during the autumn. For a series of years they were absent or found only in small numbers. In 1905, when cholera was introduced into Germany, these cholera-like bacilli were found in enormous numbers in the Elbe. In 1906 they had entirely disappeared. Haffkine has reported that he recognized in India, in the tanks in the neighborhood of which cholera had existed, abundant cholera-like vibrios, while in the tanks in neighborhoods free of cholera such vibrios were regularly lacking. In Hamburg we investigated frequently the water of the Alster, one of the small tributaries of the Elbe, without ever finding cholera-like vibrios in it.

Cholera vibrios are capable of continued existence in sterilized water for a long time. A year after the infection of sterile well water cholera vibrios still capable of developing may be recognized. Even in sterile distilled water they exist for months. The writer inoculated unsterilized Elbe water with cholera dejecta and was able to recognize cholera

vibrios still capable of developing after twenty-five days. These specimens were kept at room temperature. At the writer's suggestion, Oergel infected unsterilized Elbe water with the cholera vibrio and kept it in a refrigerator at 8° to 9° C. From this he was able after almost a year to isolate cholera vibrios capable of development. It is not proved that the cholera vibrio is able to exist as long in the free flowing water of the Elbe, but this is made probable. Hankin also reported that he could recognize cholera vibrios in a well for longer than a year. In Hamburg in 1893 cholera vibrios capable of developing could be recognized not only in the Elbe water at various points but also in the city hydrant water. Hence it must be assumed either that the cholera vibrios had persisted throughout a whole year in the Elbe or that they had been introduced anew in 1893. In both cases an increase in the cholera vibrios in the Elbe must be assumed.

In the year 1896 cholera vibrios were again successfully isolated from the Elbe water. The problem as to whether they had remained there from the year 1892 or had been again introduced was left undecided. We were able in 1893 to recognize in the Oder, where cholera had broken out, the cholera vibrios as well as in the Ruhr and in the harbor of Ruhrort when cholera prevailed there. Personally, after such findings, the writer considers it proved that the spread of cholera by water is, in our latitudes, to be regarded as dependent not only on cholera vibrios which reach the water with cholera dejecta and remain alive, but also, under favorable conditions, on their increase there. The number of instances in which cholera vibrios, capable of developing, have been recognized in wells and other sources of water-supply has increased since 1892, but they are not sufficient to decide the degree in which cholera vibrios are capable of increasing in river and well water.

Power of the Cholera Vibrio to Persist and Develop on Foodstuffs.—How far may the transmission of the disease take place by articles of food which are infected? Strong has reported that in Manila cholera is undoubtedly spread by articles of food. Instances of infection from many articles of food have been established. All the experiments have shown that the cholera vibrio lives for a relatively short time on foodstuffs. In sterilized milk they grow well, but in unsterilized milk they are destroyed as soon as the milk begins to sour, according to Kitasato. Nevertheless, Heim was able to demonstrate living cholera vibrios in milk which had been sour for six days. Since milk comes in contact with water, not only in adulteration but in the washing of the cans, great care should be devoted to it in times of epidemics. Food materials which are not handled in a cleanly way, may very well act as the transmitters of the cholera vibrio.

The Transmission of the Cholera Vibrio by Insects.—This has been investigated experimentally by a number of authors. Living cholera vibrios have been found in flies one and a half hours after they had come in contact with cholera material. Flies have been caught in the ward in which cholera patients lay and cholera vibrios found adherent to them. Further, flies were fed with cholera material, and it has been shown that their intestinal contents, examined with all possible precaution, still

showed, after fourteen days, living cholera vibrios—which doubtless indicates an increase in the fly's intestine.

Resistance of the Cholera Vibrio to Chemical and Physical Influences.—Definite resistant bodies (spores) have not yet been found, but the cholera vibrio is able not only under especially favorable conditions to persist and multiply, but to keep up the struggle for existence under quite unfavorable conditions. They show themselves, however, very slightly resistant to measures immediately directed to their destruction. *Light:* Palermo proved that sunlight does not kill the cholera vibrio as long as the cultures are kept cool, and Wesbrook confirmed this insofar as he showed that the destruction of the cholera vibrio takes place in sunshine only when air is admitted. *Desiccation:* In moist dust Germano was able to demonstrate the cholera vibrio for three months. In dry dust they died at once. According to Karlinsky the cholera vibrios remained alive on infected cloth for more than two hundred days so long as it was kept in a closed chest, but if the rags were dried before they were put into the chest the vibrios remained alive only thirty-six days. If cholera dejecta were used for such tests, instead of cultures, there appeared to be a far slighter power of resistance. *Heat:* The cholera vibrio is very sensitive to heat, and is killed by heating for ten minutes at 60° C. Similarly, the power of resistance toward chemical disinfectants is extraordinarily slight; thus, $\frac{1}{2}$ per cent. carbolic acid kills them in ten minutes; 1 per cent. in five minutes; corrosive sublimate 1 to 1,000,000 in a few minutes, hydrochloric and sulphuric acid 1 to 10,000 in a few seconds, etc.

Pathogenicity and Virulence of the Cholera Vibrio.—The cholera vibrio is virulent directly after its isolation from the dejecta of cholera patients. Koch made the gastric contents of guinea-pigs alkaline and introduced pure cultures of cholera. Others injected the cultures directly into the duodenum of the animal. In both ways a cholera-like intestinal disease could be produced. Similarly, fatal infections could be produced by subcutaneous and intraperitoneal injections into animals of pure cultures of cholera bacteria. Later, it proved possible to find animals which suffer from natural infections of pure cultures of the cholera, and Karlinsky and Metchnikoff produced a fatal infection in sucking rabbits, dogs, or cats by mixing cultures of the cholera vibrio with their milk.

Human beings have sacrificed themselves for such experiments. Macnamara made an observation in which 19 men drank water which contained cholera dejecta; 5 of them died of cholera. In the Hamburg Hygienic Institute, Oergel, who had been continually occupied in investigating cholera, died from a cholera infection at a time when there was no cholera in Hamburg. He had sucked up through a glass capillary tube a fluid rich in vibrios, and did not immediately disinfect his mouth. Several other laboratory cholera cases have been observed. It has been shown that the clinical picture of Asiatic cholera can be produced by simply swallowing cholera cultures which have been directly isolated from cholera dejecta without having undergone a ripening process of any kind. Metchnikoff succeeded in finding a bacterium which greatly increased the pathogenic action of the cholera organism. This has no

general significance because it is in the most intense cases that cholera vibrios are found in the intestine without associated bacteria.

Cholera Toxins.—Does the cholera vibrio set up a pure infection or produce, as Koch maintained from the beginning, a toxin? Gruber and other investigators held to the idea that the cholera vibrio acted as a purely infectious agent, and produced no toxins. R. Pfeiffer, however, showed that animals would die after inoculation with killed cholera vibrios. He filtered actively poisonous cholera cultures and showed that the bacterium-free filtrate was not poisonous. From this he concluded that the cholera poison adheres closely to the bodies of the vibrios but was not excreted by them, a view which many other investigators had taken. According to R. Pfeiffer, the symptoms are produced by the destruction of cholera vibrios in the body through which the poison is set free. In 1905 Kraus and Pribram obtained a toxin from cultures which killed rabbits in a few minutes. This was only done with certain cultures, not with all, which explains Pfeiffer's earlier negative results. Kraus has obtained a specific antitoxin.

Immunity.—Gruber holds that in the case of cholera we must be dealing with an infection and not an intoxication, because it is not possible to immunize the animals against the poison but only against the infection. If one inoculates animals, *e. g.*, guinea-pigs, rabbits, etc., repeatedly with the cholera vibrios, they show themselves not much more resistant to larger amounts of killed cholera vibrios than normal animals. But the immunity becomes evident when one injects large masses of living cholera vibrios, which would surely kill normal animals, into these animals previously treated with cholera vibrios. If cholera vibrios be injected into animals which have been treated with quantities of cholera vibrios which are not lethal, the cholera vibrios, as R. Pfeiffer has shown, are gradually destroyed in these specifically immune animals. Within a few minutes they are changed into minute particles or granules and killed. The further formation of poison is thereby inhibited. In animals which are not immune an active increase of the injected cholera vibrios may be observed.

Pfeiffer's Reaction.—R. Pfeiffer was further able to show that only cholera vibrios are influenced in this way in cholera immune animals and not other vibrios, not even those vibrios which cannot be distinguished morphologically and culturally from cholera vibrios. Through this discovery he assisted in a difficulty which was becoming awkward. In 1893, numerous vibrios occurred in the water of the Elbe, which resembled precisely the cholera vibrios. The question arose as to whether the inhabitants were to be warned against the use of the hydrant water. By Pfeiffer's method it was possible without difficulty to prove that the majority of the vibrios found in the water of the Elbe were not to be regarded as cholera vibrios. Pfeiffer was successful in making his specific immune reaction more practically useful by the discovery that it is sufficient to mix a small quantity of blood serum of cholera-immune animals with the cholera vibrios in order to change them into granules and dissolve them even in the bodies of animals which had not been so treated before. Bordet showed that Pfeiffer's reaction occurs also

in the test-tube if a small quantity of fresh normal blood serum is added. One can thus observe Pfeiffer's reaction outside the animal body. The establishment of this fact simplifies the technique still further.

Agglutination.—If cholera vibrios be mixed with cholera immune serum the cholera vibrios become non-motile and accumulate in little clumps. By this it was finally possible to exclude the group actions and to distinguish with certainty cholera vibrios from cholera-like organisms. For this purpose only those sera were used which caused distinct agglutination within a few minutes when diluted many thousand times. The writer has made extended investigations to decide this point, in connection with cholera vibrios of wide origin. These have shown that the agglutination method is specific as long as bacteria are used which are not agglutinated by physiological salt solution or diluted normal serum. In other laboratories such universally good results have not been reached, but the unfavorable results are dependent upon the use of unsuitable culture media or upon some injurious influences. These new methods enable us to distinguish rapidly and with certainty the cholera-like vibrios obtained by means of the peptone preliminary culture from the true cholera vibrio. It is, in addition, even possible to test the blood-serum of persons suspected of an infection with cholera as to whether it shows the specific cholera immune bodies. This has been very serviceable in suspected cases.

Cholera Antitoxin and Vaccination.—After all efforts to produce an effective specific antitoxin for cholera had failed, cholera cultures have been injected for prophylactic purposes, analogous to Pasteur's vaccination, into persons who were especially exposed to infection. It has been applied by Haffkine in India, with in part favorable results but this preventive inoculation only influences infection. Anticholera serum is useful in animals but has not been of much value in man. By the inoculation of virulent cholera one may, according to the results of Pfeiffer and Kolle, produce an effect which may be recognized even after a year by the presence of the immune substances in the body of human beings and animals thus treated.

Pathological Anatomy.—Bodies in the algid stage present a dusky gray-blue color. The lips, eyelids, and feet are often blackish blue; the countenance is pale and sunken; the eyes are half open. The skin, loose and wrinkled, can easily be lifted. The abdomen is generally contracted and of a pasty consistence. Rigor mortis is marked. The fingers are often tightly bent and postmortem twitchings are frequent.

The subcutaneous tissue is dry; the musculature shows no striking change, nor is any characteristic alteration to be found in the central nervous system, except for the occasional congestion. The lungs frequently show lobar pneumonia, which may be observed from the third day of the disease, pulmonary œdema, and hemorrhages into the tissues. The heart muscle in many cases shows considerable degeneration with slight cloudy swelling. The condition found in the peritoneum and in the intestinal tract is most characteristic. In a person dying in the attack, the small intestine presents a rose-red color, with great injection of the vessels and a ropy coating. The extent to which the intestinal

loops are filled varies. Empty convolutions alternate with those which are distended and whose opaque white contents shimmer through. The intestinal contents are usually like rice-water, but sometimes colored with bile or blood, though at times simply diarrhœal.

The intestinal mucosa is sometimes of normal color, but as a rule is reddened and œdematous. But often, as for example in the later stages, in consequence of diphtheritic or necrotic processes, it is blackish red, with ecchymoses. The mucosa is as a rule deprived of its epithelium throughout considerable portions. The solitary nodules are swollen and show generally small hemorrhages in the centre. These changes are especially definite in the small intestine, particularly in the lower ileum, but they occur sometimes in the colon. Koch determined that the vibrios penetrate into the tubular glands of the intestinal mucosa and there produce an extreme irritation. Often the vibrios were found behind the epithelium of the gland. On the surface of the villi they are to be found in great numbers. With bloody infiltration of the mucosa, the bacteria are found in the deeper layers, in places even penetrating the musculature of the intestine. The chief seat of the invasion is in the lower ileum, where the most intense anatomical alterations are found. In the diphtheritic processes the mucosa of the intestine exhibited a deep necrosis, with serous infiltration and swelling of the submucosa and muscularis.

The kidneys are intensely affected even as early as from four to nine hours after the onset. Macroscopically at that stage no alteration is found, except the opacity of the labyrinthine portion of the kidney; but microscopically, extraordinary swelling of the epithelium of the convoluted tubules may be observed. The portion of the cell body turned toward the lumen presents a sieve-like perforated appearance. The nuclei are seldom altered, as a rule only the cell protoplasm. Later there is a complete dissolution of the cells. From the second to the fourth days of the disease the kidneys show great congestion, so that the cut surface appears dark grayish red, and in the border zone shows a dull red color. Microscopically the glomeruli and intertubular capillaries are filled, and in the secreting parenchyma the plasmolysis is much farther advanced. After the third week the regeneration of secretory renal epithelium begins. The bladder is strongly contracted and contains only a little turbid urine loaded with casts.

The spleen is as a rule but little altered, although multiple hemorrhages may be found in it. In the liver, beside slightly cloudy swelling of the parenchyma, there are seldom any changes. During the first days of the disease the gall-bladder contains a very little dark thick bile. Subsequently the bile is more liquid and clearer.

The blood, spleen, kidneys, and liver are as a rule free from bacteria. In the lungs foreign microörganisms occur. Rekowski reports, however, that in 14 cholera autopsies he found the cholera vibrios in the liver, kidneys, and heart.

Incubation.—At the beginning of a cholera epidemic one observes, beside the extraordinarily rapidly fatal cases of the disease, all gradations down to scarcely recognizable diarrhœa. These latter occur much

more frequently than had been generally supposed. Cases also occur in which no symptoms whatever appear and only the discovery of the living cholera vibrios in the dejecta shows the existence of the infection. Many observations show that, following an indiscretion in diet, or emotional disturbances, rapid and unexpectedly severe choleraic symptoms may appear. It is clear from this that no unanimous results can be reached as to the incubation time. Based on results from individuals who came from cholera-free places to infected localities, it has been determined that the disease appears as a rule two and a half to five days after their arrival. The individuals who drank cholera vibrios sickened, at the earliest, twelve hours afterward. In epidemics the disease frequently appears twenty-four hours after the opportunity for infection. On the other hand the incubation period may last from eight to fourteen days. As a rule the incubation period lasts from two to three days, but if one reckons the slight prodromal diarrhœas, it must be regarded as shorter.

Symptoms.—At present five forms of cholera are distinguished:

1. **Cholera Infection without Definite Symptoms.**—Here living cholera vibrios are found in the liquid, semisolid, or even solid stools of completely healthy persons who show no symptoms, or scarcely noticeable symptoms, of intestinal disturbance. Under unfavorable conditions these may pass on into the more severe forms, but it many cases the cholera vibrios soon disappear from the stools without definite disease having existed.

2. **Cholera Diarrhœa.**—In this more or less frequently yellowish stools, colic, flatulence, coated tongue, thirst, and a feeling of pressure in the region of the stomach are observed. The condition may be recovered from in a few days or it may become more severe.

3. **Cholerine.**—This is characterized by rice-water stools, vomiting, and general disturbances. Forms 2 and 3 were previously described together as the first stage of cholera and spoken of as prodromal diarrhœa.

4. **Pronounced Cholera.**—This was previously called the second stage.

5. **Stadium Comatosum.**—The patient shows extreme intoxication with cessation and decrease of the stools and vomiting, sometimes with fever, but oftener with subnormal temperature; he becomes somnolent, delirious, and comatose. Frequently anuria appears, which is an unfavorable sign, as is also a subnormal temperature. The forms with fever often result favorably. The cholera diarrhœa may sometimes pass directly into the stadium comatosum without there having been at any time a typical attack of cholera. Since the cholera vibrios may be demonstrated so long as the third or fourth week of the disease, it is not impossible that the stadium comatosum is to be regarded as a sort of chronic cholera.

Since the mildest cases differ not at all from an ordinary diarrhœa, we need only concern ourselves with a typical pronounced case of the disease. This presents the following symptoms: In the first part of the so-called prodromal stages thin, fluid masses of normal color are discharged without pain or straining, although there are some colicky pains in the abdomen. At times loss of appetite, slight feelings of nausea,

dulness, and lassitude are present. The hands and feet may be cold. These symptoms may disappear in one or two days or the condition may become suddenly worse and the second stage develop (the true cholera attack), with unusually thin fluid stools, rapidly following one another without any tenesmus. In the beginning the discharges are bile-stained, but later they become colorless and have a watery appearance, rendered turbid by grayish-white flecks—the rice-water stools.

Simultaneously vomiting sets in. At first everything the stomach contains is ejected; then the vomitus assumes the character of the rice-water stools. Often there is singultus. The appearance of the patient changes rapidly; the skin becomes lax and wrinkled, and when folds are pulled up they disappear slowly. The nose becomes thin and pointed, the eyes sink deep into their orbits, and the cheek bones stand out prominently. This is the *facies cholerica*. The heart impulse, the heart sounds, and the pulse become weaker; the nose, ears, and extremities feel cool; the skin assumes a dark gray color; grayish-blue rings appear around the eyes; the lips become bluish, as do also the hands and feet, especially around the nails. The secretion of urine gradually ceases; torturing, unquenchable thirst ensues; cramps appear in the calves, in the thigh muscles, and in the muscles of the arms and abdomen. The reflexes are greatly diminished; the pupils react only slowly. The voice becomes hoarse and toneless. A sensation of suffocation arises. The patient is completely exhausted, complains of faintness and palpitation of the heart as well as confusion, anxiety, and a feeling of heat, although the surface temperature is subnormal, while in the rectum it may be 104° F. The greater the difference between these two temperatures the more unfavorable the prognosis. Consciousness remains complete, but the patient sometimes becomes apathetic. In the most severe cases the disease passes on into the third stage (stadium algidum), which in the great majority leads to death. This stage is characterized by almost complete cessation of circulation. The action of the heart is weak and irregular; the first sound is impure, the second often inaudible; the radial pulse almost impalpable. If a well-filled vein be cut, dark and thick blood flows which does not become lighter in the air. In the worst cases no blood flows at all, even if arteries are cut. The breathing is labored; the skin is moist and cold, often covered with sticky perspiration. The skin is lead-gray; the fingers, toes, and ears, dark violet; the discharges decrease gradually; the patient is completely voiceless; dark spots appear on the conjunctivæ, and the cornea becomes opaque. Friction murmurs appear in the pericardium and pleura as a result of lack of moisture. Consciousness is still present but dulled. Violent thirst, precordial distress, and a feeling of depression persist. This death-like condition gradually passes into real death, sometimes only a few hours after the beginning, but often not until the second day. Recovery after this stage seldom occurs.

The Stage of Recovery (Stadium Restitutionis or Reactionis).—The vomiting ceases, the stools become less frequent, of greater consistency, and gradually assume a bile-stained appearance. The symptoms described gradually disappear. In less severe cases complete health may

be recovered in a few days; in others convalescence is long and the heart action remains weak and variable. The urine contains large amounts of albumin. Sometimes febrile periods occur—the reaction fever, which lasts for one or more days, with rapid pulse, dull heart sounds, headache, and even delirium and somnolence. While exanthems do not appear in the height of the attack, the most various changes in the skin may be observed in the stage of restitution. These may be bluish-red spots or swollen red flecks forming a rose-color rash and larger erythema-like patches of red color and of various forms which may be spoken of as *erythema annulare*. Sometimes also nodules are seen, the *roseola papulosa* or urticarial wheals may form. Finally there may be extensive reddening and swelling which resembles erysipelas. Small hemorrhages, larger vibices, and sugillations may appear or vesicular eruptions and wheals. These exanthems occur most frequently on the extremities. In convalescence there is a tendency to the formation of furuncles.

Cholera was previously considered as a general disease chiefly on account of the exanthems observed in its course, but is now regarded as a local infection of the intestinal tract with a consequent intoxication. Symptoms have been observed also in diseases which begin with a great loss of fluid, which have the greatest similarity to those of the severe types of cholera. According to some the majority of the symptoms of cholera may be explained by a simple loss of water which results from the action of the toxin. In the stage of collapse there is a marked loss of water and salts (chlorides). In the later stages the water may be regained but not the salts and so the blood is hypotonic.

Against this intoxication theory, the objection is that the most severe symptoms appear at a time when the intestinal mucosa is so altered as to be incapable of absorbing any poison, but before the destruction of the mucosa sufficient poison may be absorbed to explain these phenomena. There was a tendency to explain the exanthems as due to circulatory disturbance. This might be true in the case of the bluish patches and gangrenous processes, but most of the other exanthems are probably the direct result of the action of the toxin.

Complications and Sequelæ.—In many patients complications appear which are a more or less direct result of the disturbances caused by cholera intoxication. Besides the nephritis, the exanthems, the diphtheritic inflammations, and the hemorrhages, which occur in all mucosæ, pneumonia and infarcts in the lung, spleen, kidneys, and other organs may also occur. In rare cases pleurisy, peritonitis, meningitis, abscess formation, bronchial catarrh, catarrhal cystitis, icterus, and venous thrombosis occur. In many patients anemia, emaciation, and general debility, especially in the digestive functions, follow. In certain cases this may amount to marasmus, and in rare cases mental weakness or even insanity, generally of a melancholic character, may appear.

The most frequent and characteristic sequel is the "*cholera typhoid*," which occurs in about one-quarter of all severe cases in the second half of the first week. General debility and exhaustion appear with a special limitation of the psychical functions. Apathy, sleepiness, headache, serious disturbances of consciousness, delirium, a soporous condition,

even amounting to deep coma, occur. Cramps in different muscles are frequent; generalized convulsions are less common. The tongue and lips are dry and cracked, often with blackish sordes. Rales are to be heard throughout the lungs. There may be considerable elevation of temperature and frequently a dicrotic pulse as well as quickened breathing. Some explain the "cholera typhoid" chiefly as a result of poisoning with cholera toxin. But undoubtedly the action of foreign bacteria is important. In some cases uremia forms the basis.

Diagnosis.—Practically the only disease which gives difficulty is the so-called *cholera nostras* in the severe form sometimes seen in temperate climates. The symptoms are in no way different and a positive diagnosis can only be made by bacteriological methods. It is important that these should be applied promptly in any doubtful case.

In the Living Subject.—About 50 cc. of the dejecta are taken without the addition of any disinfectant. A number of cover-slips are smeared with the dejecta, preferably with a particle of mucus, for microscopic investigation. When possible several agar cultures are to be made on the spot. Linen freshly soiled with dejecta is treated in the same way.

From the Cadaver.—The peritoneal cavity is opened and three loops of intestine, 15 cm. long, are ligated at each end and taken out; one is from the middle part of the ileum, one about 2 meters above the ileocecal valve, and one immediately above it. The last mentioned is the most important. Thick-walled bottles with boiled corks may be used for sending this material. These bottles must be freshly boiled and must not come into contact with disinfectants. The microscopic examination is made with smear preparations and hanging drops are prepared with peptone solution, and these are to be examined immediately, and after half an hour's incubation at 37° C.

Two series of gelatin plates are prepared, of which the original plates are to be smeared with a small fleck of mucus or with a loop full of the material. The gelatin plates are best incubated at 22° C. After eighteen hours the examination may begin with the use of a cover-glass preparation. The agar plates may be examined after remaining from eight to twelve hours at 37° C.

Peptone Culture.—Reagent glasses with 10 cc. of peptone solution are infected and, after remaining from three to twelve hours at 37° C., examined microscopically. If cholera-like vibrios are found on the surface, agar and gelatin plates are made from this culture. Further, small vessels with 50 cc. peptone solution and 1 cc. material are prepared and, after being incubated at 37° C. for from three to twelve hours, are examined. From the plates suspected colonies are transplanted on agar. After the development of these the agglutination test is carried out. Water suspected of being infected is made into a 1 per cent. peptone solution by the addition of concentrated peptone solution in quantities of 50 cc. to 1 liter of water. After remaining from eight to twelve hours at 37° C. this is examined in the same way as the peptone preliminary culture. In 1905 the writer added cholera serum directly to a fleck of mucus or to a drop of the dejecta and thereby was able at

once to declare cases as not being cholera, although the dejecta contained cholera-like vibrios and the patients had suspicious symptoms. The negative results were confirmed later by other methods.

With the first case of the disease in a locality all methods of investigation described must be made use of. After the presence of the cholera vibrios is established the investigations may be considerably curtailed.

Interpretation of the Results.—The diagnosis is regarded as certain when all the morphological and cultural characteristics are met with and the agglutination test as well as Pfeiffer's reaction are positive. Convalescents are to be regarded as no more infectious when the examination has proved negative on three days, each separated by one day.

Treatment.—In cholera without symptoms, *i. e.*, in the mild diarrhœas, it is necessary to provide a regular mode of life, and prevent excess of every kind, especially in eating and drinking. The use of *opium* has not always proved rational. After a transient cessation of the diarrhœa severe disturbances often appear. Koch used opium to quiet the intestines of the animals experimented on, and in this way gave the cholera vibrio an opportunity for multiplying. With the hypodermic use of morphine a favorable influence on the circulation was in many cases brought about.

Specific antiseptic materials which might be expected to inhibit the growth of the cholera vibrios in the stomach and intestines have been without value. We have fallen back on materials which cause the organisms to be forced out of the intestinal canal. Castor oil and especially calomel have been used. According to Rumpff, it is best to give 0.03 to 0.05 gm. (gr. $\frac{1}{2}$ to $\frac{3}{4}$) of calomel every two hours for one or two days. In this way the adult takes a maximum of 0.6 to 1.0 gm. (gr. 9 to 15). For children the dose is to be correspondingly diminished. If the pulse of the patient become rapid and small the hypodermic injections of morphine prove helpful.

In well-marked cases the vomiting interferes considerably with the treatment. Sometimes this may be temporarily stopped by the administration of small pieces of ice. In other cases a quieting of the stomach must be attempted by narcotics. Injections of morphine of 0.005 gm. (gr. $\frac{1}{12}$) and more are recommended for this. The vomiting and cramps may be relieved and also the excitement and the subjective disturbances. Hot baths affect some patients favorably, but they must be interrupted if attacks of fainting or collapse appear. In individual cases it was observed that the cholera exanthems developed as an immediate consequence of the hot baths; in other cases the blue-gray color of the skin disappeared, as well as the cramps; the pulse improved and convalescence set in. In many cases it is necessary to give several baths.

When the pulse becomes small and the heart sounds weak, camphor oil should be given hypodermically. Fluid can be given by intravenous or subcutaneous injection of salt solution. Sometimes after the intravenous injection of a liter of fluid at about 40° C. the pulse improves, the respirations become deeper, the somnolence disappears, and the skin assumes a reddish color. The method of intravenous infusion advised by Rogers has proved of great value. He uses a hypertonic

solution composed of sodium chloride, 120 grains; potassium chloride, 6 grains; calcium chloride, 4 grains; water, 1 pint. Four pints (2000 cc.) are given slowly into a vein; this should be repeated as is indicated. Cantani, who recommended an enema of tannin, prefers subcutaneous injection to the intravenous, because the mixture with the blood takes place more slowly and thoroughly. In the stadium comatosum, baths up to 35° C. with subsequent packs in woollen blankets, as well as sweat baths, after abundant administration of milk and water, are recommended, but the results are seldom favorable.

Measures for Combating the Epidemic.—Before everything, it is important to recognize at once the first case of the disease and to take measures to prevent its transmission and spread. It is the duty of every physician to see that in every suspicious case there is at once an expert examination of the dejecta for the cholera vibrio. Until the examination is completed the patient is to be treated as if he really had cholera.

As soon as Asiatic cholera is recognized all efforts must be turned toward the discovery of the source of infection. In most countries the measures which must be carried out on the appearance of cholera are defined by law. If these measures are conducted in such a systematic way as they were in the years 1893–94, and especially 1905, in Germany, we shall not have much more to fear from Asiatic cholera in Europe and America, and it might then be considered as the disease of the nineteenth century. Unfortunately many countries are not so well prepared for the struggle as Germany, and one can not everywhere depend on finding the necessary coöperation. The brilliant success in Germany was due entirely to Koch's logical plan of fighting the disease. He stated that "however simple or complicated one may regard cholera, there is always a chain of circumstances which is sometimes short and sometimes very long. As soon as we succeed in breaking a single link in this chain, the chain, whether long or short, must break. That link of the chain which we know most exactly and against which we can act most successfully is the cholera vibrio."

The cholera germ is present in a condition capable of producing infection in the intestinal contents of persons suffering from cholera; it may also be found after recovery from the disease, and may also occur in individuals exposed to infection although they show no symptoms of the disease. In order to start a new infection the cholera germ must, without having previously become dry, gain entrance into the digestive tract of a susceptible individual. Direct transmission is more frequent the more unclean the surroundings of the patients. With sanitary surroundings such transmission may be prevented. Soiled clothes are especially to be considered, as well as the infected persons themselves, in the transmission of the germ. The most usual medium for transportation is water, on the one hand, because it preserves the germ well, and on the other hand because it is more readily defiled by cholera dejecta than any other one food material. Besides, water most easily carries the cholera germ uninjured through the stomach. The safest guard against cholera is in the abundant provision of unquestionably good water, as well as careful removal of fecal material and garbage.

In communities whose water supply is perfectly good one may without great difficulty prevent the introduction of the cholera germ.

As to the conditions of life, much can be done in a preventive way. Where people live crowded together in a dark dwelling, the disease finds its most favorable soil and forms foci and spreads uncontrollably. Less is to be expected of limitations of intercourse. Transportation of freight may be allowed to go on freely and the transportation of people may be limited merely to their undergoing medical supervision. Even persons coming from an infected region may enjoy unlimited freedom as long as some supervision is kept over them. In the case of homeless people, tramps, etc., who have been shown to be especially prone to cholera infection, a more thorough control is justified. This is true also of immigrants who come from infected regions. Further, the crews of river boats are to be carefully watched in time of cholera infection. The value of a quarantine for foodstuffs is not commensurate with the injury that arises from such a measure. Each person, however, should make a rule to eat nothing uncooked that does not come from a thoroughly trustworthy source.

For ships, instead of quarantine, a medical review together with rational methods of disinfection is suitable. Suspicious persons only should be kept under observation, and these for not more than five days. In view of such measures we may throw aside completely the system of hushing up cholera epidemics formerly so much adopted.

In Germany the central boards of health have sent especially trained physicians and nurses to infected places. The patients must be at once isolated. The disinfection of dwellings may be limited to the excreta and objects that have been soiled. Infected, overfilled, and miserable dwellings should be cleaned out on the appearance of cholera.

Disinfection.—The following are to be considered as disinfectants: cresol water ($2\frac{1}{2}$ per cent.), carbolic acid solution (3 per cent.), chloride of lime (1 to 50), milk of lime 1 to 5, formaldehyde, and disinfection by steam in suitable cases by boiling. The dejecta are mixed with equal quantities of the above-mentioned fluids and after two hours the disinfection may be regarded as complete. For the disinfection of soiled clothes, cresol water is recommended. For the disinfection of dirty water, chloride of lime and milk of lime are useful; for closets, cresol water and milk of lime; for privy pits, chloride and milk of lime.

The disinfection of the hands and other parts of the body may be accomplished by cresol water and carbolic acid solution. Bed linen and underclothes, washable pieces of clothing, etc., are to be boiled or placed in carbolic acid solution for a period of two hours. Pieces of clothing which cannot be washed, mattresses, carpets, etc., are to be disinfected by steam. The surroundings of the patient are to be washed with cloths soaked in cresol water or carbolic acid solution. It is necessary to disinfect the place where the patient or corpse lies and the neighborhood for a distance of about two meters. Leather, wood and metal structures are washed thoroughly with carbolic acid solution or cresol water.

PLATE XVI

FIG. 1

FIG. 2

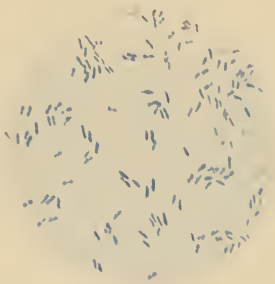


FIG. 3

Fig. 1.—Slide prepared from a culture from a non-diphtheritic throat.
Fig. 2.—Diphtheria bacilli stained by Loeffler's method.
Fig. 3.—Diphtheria bacilli stained by Neisser's method.

FIG. 4

FIG. 5

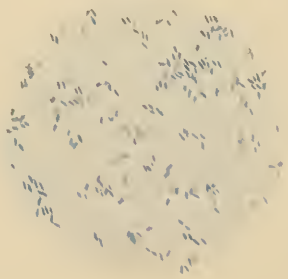


FIG. 6

Fig. 4.—Diphtheria bacilli stained by Hunt's method.
Fig. 5.—Diphtheria bacilli of the short variety.
Fig. 6.—Diphtheria bacilli of the long variety.

CHAPTER XVIII

DIPHTHERIA

By JOHN H. McCOLLOM, M.D.

AND

EDWIN H. PLACE, M.D.

Definition.—An acute infectious and contagious disease, generally of the air passages, characterized by the presence of a patch of dirty white or grayish membrane, cultures from which show a bacillus known as the Klebs-Loeffler or the *Bacillus diphtheriæ*. The terms membranous croup, suffocative catarrh, and angina maligna are misnomers, and should not be used. It is important to emphasize that diphtheria at the outset is a local manifestation and that the constitutional symptoms which occur later are due to the absorption of the toxin generated by the specific organism.

Etiology.—Many different theories have been advanced regarding the etiology of diphtheria. Soil moisture, sewage gas, imperfect drainage, poor hygienic surroundings, overcrowding, have been supposed to be important factors, but although these conditions may have a predisposing influence, they never of themselves can originate diphtheria.

It was not until 1883, when Klebs demonstrated a small bacillus in the false membrane of diphtheria, that the etiology was placed on a scientific basis. Loeffler in 1884 isolated and cultivated this organism; hence the term Klebs-Loeffler bacillus. Darier in 1885 independently arrived at similar results. Roux and Yersin found this bacillus in all cases of diphtheria. It is a short rod, straight or slightly curved, with a diameter of 0.5 to 0.8μ and from 2 to 3μ in length. This organism grows on all the usual culture media. It is aërobic, non-motile, and non-liquefying; it grows characteristically on Loeffler's blood serum. This culture medium should be neutral or very slightly alkaline. If it is acid or strongly alkaline the organism will not grow satisfactorily. The bacillus of diphtheria grows more abundantly at the temperature of the body than at room temperature. Cold inhibits its growth but does not destroy its vitality. Under suitable conditions its vitality may be retained for a long time, but as it has no spores it can be easily destroyed by different germicides. Welch and Abbott found the thermal death-point to be 58° C. for ten minutes.

The bacillus of diphtheria can be stained with the common aniline dyes, but Loeffler found that an alkaline methylene blue was the most satisfactory stain. The composition of this is as follows: saturated alcoholic methylene blue 30 parts and a watery solution of potassium hydrate (1 part to 10,000) 100 parts. (Plate XVI.) Hunt's method

of staining is as follows: (1) Stain in a saturated aqueous mythelene blue one minute without heating; (2) wash and dry; (3) cover with a tannic acid solution, 10 per cent., for one minute; (4) wash; (5) stain in an aqueous methyl orange solution one minute; wash and dry. When a preparation is stained in this way the polar granules are distinctly seen as small dark blue points and the body of the organism is of a light-orange color. These differential stains are of great assistance in deciding the character of doubtful bacilli.

The morphology varies markedly under different conditions of growth, such as temperature, the admixture of other organisms, the character and reaction of the media, and especially with the duration of the growth. For a few hours (four to six) after planting the bacillus often appears as a short, rather plump, evenly stained rod. After twelve hours' incubation irregularity of the protoplasm appears, and the deeply stained polar bodies begin to show. The organism is longer and more slender. After eighteen to twenty-four hours the smear is usually most characteristic, presenting slender rods, with deeply stained bipolar bodies, arranged parallel or at an angle forming a "V." Bizarre (involution) forms, with large swollen ends, occur especially in old cultures. Branching is seen occasionally. Barred and banded forms also occur.

Virulence.—The diphtheria bacillus is highly toxic for some animals, especially guinea-pigs. Some strains are only slightly toxic, but the toxicity may be raised by passage through susceptible animals or birds, and by growing with other organisms such as streptococci. Entirely non-virulent bacilli, according to present evidence, cannot be made virulent. Bacilli morphologically and culturally like the *Bacillus diphtheriæ* may be found in diseased or normal throats but are non-virulent. It has been shown by L. Martin that bacilli which are non-virulent for guinea-pigs may still produce diphtheria toxin in culture media. What effect such organisms might have on human beings cannot be said.

Similar Organisms.—Various bacilli are found in throat, nose and ear cultures, as well as from other sources, which resemble the diphtheria bacillus. The pleomorphism of the diphtheria bacillus makes this even more confusing. Hofmann's bacillus is the least like the diphtheria bacillus of this group. It is a short evenly stained, rather plump bacillus growing readily with an opaque whitish growth. It does not produce toxin and is non-virulent for guinea-pigs; develops no polar bodies, and has no tendency to bizarre involution forms. It does not ferment any of the sugars. It is found more frequently in the nose than throat. The bacillus xerosis may have the same morphology as the diphtheria bacillus, but is more likely to be barred. It may be impossible to distinguish them except by sugar fermentation and virulence tests. Its growth on blood serum is usually scanty nearly colorless to white. It is non-virulent. It ferments saccharose but not dextrine. There are other bacilli which have resemblance to the Klebs-Loeffler, which come into this group biologically, but their exact relationship is not known.

Susceptibility.—The young are particularly susceptible. The incidence under one year is relatively low, being about 2.75 per cent. of our cases. This is ascribed to (1) slight chance of infection, (2)

acid reaction of the mucous membranes at this age, (3) immunity from the mother's milk in breast cases, (4) slight development of lymphoid tissue, which is so often the point of infection. The disease occurs frequently in infants in asylums. Adults although much less frequently attacked have little real immunity. There is some immunity following an attack, at least when antitoxin is given, but it is slight and of short duration. Second attacks are not rare and may occur within two weeks. Repeated attacks are due to a vulnerable mucous membrane.

Adenoids and hypertrophied tonsils increase the susceptibility of the individual, and when these conditions obtain the importance of operative interference is evident. Measles especially increases the susceptibility probably from the numerous breaks in the continuity of the mucous membranes. Diphtheria is especially likely to occur where the mucous membranes are not normal and local resistance seems to be of more importance than general or specific immunity. After operations on the throat and nose, diphtheria occurs readily, if the patient be exposed and non-immunized. An individual who is subject to repeated attacks of tonsillitis is particularly susceptible to diphtheria. The general condition has no influence on susceptibility. The most robust are just as likely to contract the disease as the most delicate.

Pathology.[1]—The essential lesions may be divided into two kinds: local lesions, characterized by the formation of a membrane, and due to the immediate presence of diphtheria bacilli and the direct action of the strong toxic substances secreted by them, and general or systemic lesions due to the absorption of these toxic substances and their passage in a more dilute form in the lymph along the lymph vessels, and in the blood throughout the general vascular system. In addition there often are lesions of a third kind due to secondary infections by other bacteria, which may complicate both the local and the systemic changes,

The local lesions begin most frequently in the fauces (tonsils), the larynx, or the nares, rarely in the conjunctiva. From these primary foci the process often extends to the uvula, the pillars of the fauces, the posterior wall of the pharynx, the trachea and lungs, or to the accessory sinuses of the nose. More rarely it extends to the œsophagus, the tongue, the skin around the nose and mouth, the conjunctiva through the lacrymal ducts, or to the middle and external ear through the Eustachian tube and a perforated membrana tympani. Still more rarely, diphtheria bacilli produce lesions in the stomach and duodenum, or on the genitals (vulva, vagina, penis).

The local lesions show in all situations essentially the same pathological processes; namely, degenerative changes in the epithelial cells and in the underlying tissues, combined with an abundant fibrinous exudation from the bloodvessels. As a result of these degenerative and exudative processes separately or combined, a membrane is formed on the epithelial surface affected.

The degenerative changes in the epithelial cells in the primary lesions

[1] This section was written by F. B. Mallory, M.D.

vary greatly in extent and character, but those most noticeable are multiplication of the nuclei by direct division (an early change), necrosis of cells with hyaline transformation or with disintegration of the cytoplasm and fragmentation of the nuclei, and desquamation of cells. The hyaline transformation of cells may take place either before or after desquamation. Necrosis with fragmentation of the nuclei is always most evident in the mucous glands where it forms a pronounced and almost specific process. As a rule, the epithelium is absent beneath the membrane, although in places small masses of epithelium consisting of the lower layers of cells may be found, and occasionally the membrane may stretch over a considerable area of epithelium in which only the upper layers of cells are absent. The degenerative changes which take place in the tissues beneath the epithelium consist chiefly of necrosis of cells and of a hyaline fibrinoid change in the connective tissue and in the walls of the bloodvessels, but the process is not specific for diphtheria.

The inflammatory exudation is always marked. The fluid portion is apparently rich in fibrin factors, since, wherever it comes in contact with necrotic epithelial or other cells, it produces fibrin. As a result an abundance of fibrin is found on the epithelial surfaces and to a less extent in the underlying tissues. The cellular elements of the exudation consist at first chiefly of polymorphonuclear and endothelial leukocytes, together with a larger or smaller number of red blood corpuscles, but in the later stages numerous lymphoid and plasma cells appear. Most of the leukocytes pass to the surface and are found chiefly in the meshes of the membrane, but the lymphoid and plasma cells usually remain in the underlying tissues.

The membrane appears macroscopically at first grayish-white in color, but may change to a dirty-gray, yellowish-gray, grayish-brown, or almost black color. It may occur in isolated patches or as a continuous layer; as a thin pellicle or a thick membrane. It may be granular and easily broken up, or dense and elastic so that it can be removed in large patches. Removal of the membrane from the trachea or larynx, even when it is thick and adherent, rarely leaves a loss of substance extending into the subepithelial connective tissue. The tissue beneath the membrane and in its vicinity is always intensely injected and often hemorrhagic.

Very thick masses of membrane may be formed by the constant addition of fibrinous exudation. In the later stages of the disease the membrane may disintegrate and be broken up into a mass of detritus, or it may be cast off as a whole by being elevated by an exudation beneath it. Microscopically two forms of membrane are recognized, the fibrinous and the hyaline. The fibrinous membrane often occurs in a pure condition, especially in certain situations such as the trachea; but the hyaline membrane usually, perhaps always, occurs in combination with the fibrinous. The fibrinous membrane is characterized by greater friability than the hyaline. The fibrin appears as a reticulum of which the fibers vary much in size and in which the spaces are rather large, more often oblong than round, and with the long diameter parallel with the surface. The fibrinous membrane is not always limited to the

surface. It is often connected with masses of fibrin in the underlying tissues, and if these tissues undergo a hyaline fibrinoid change, they may lose their identity more or less completely and unite with the membrane to form a part of it. Such adhesions between the fibrinous membrane and the underlying tissues are more common over surfaces covered with pavement epithelium than in the trachea.

The hyaline membrane is dense, firm, and elastic, and can be stripped off in large flakes. It is most often found on those surfaces which are covered with pavement epithelium, *e. g.*, the tonsils. The spaces enclosed by the reticulum are small and vary but little in size; they may be angular or round. Few cells are enclosed in the spaces. The hyaline membrane arises in two ways: by fusion of hyaline degenerated cells with disappearance of the nuclei, or by fibrin forming around and fusing with cells which undergo hyaline change. The cells which undergo this hyaline transformation usually are epithelial cells, but leukocytes may undergo the same change, in which case the spaces in the reticulum are smaller.

Diphtheria bacilli are found, usually in clumps of various sizes, chiefly on the surface of the membrane, but they occur also to some extent in the necrotic tissue, and rarely enclosed in leukocytes and necrotic epithelial cells. While the diphtheria bacillus is confined for the most part to the local lesions, it sometimes gains access to the general circulation and gives rise to a septicemia. Very rarely it gives rise to localized lesions, for example, acute endocarditis. For the most part it remains in the general circulation, and simply increases the amount of toxins in the blood.

The local lesions produced by the diphtheria bacillus are often complicated by secondary infections with other bacteria, especially with the *Streptococcus pyogenes*. These may cause extensive necrosis and ulceration, gangrenous processes in the throat or extensive sloughing of the tissues of the neck.

The lesions of the lungs, although usually due to secondary infections. must be considered in connection with the local lesions, partly because they often are due in some measure at least to the immediate presence of the diphtheria bacillus, partly because the systemic lesions in the lungs are of little significance. The lesions of the lungs are the most frequent and serious which accompany diphtheritic infection and many cases are so extensive that death may be considered as due rather to the condition of the lungs than to the throat affection. While the antitoxin treatment may lead to the disappearance of a diphtheritic membrane, it cannot influence a streptococcus or pneumococcus infection.

The most common lesion is bronchopneumonia. It may be limited to single acini, to lobules, or to groups of lobules. There is but little lateral extension of the infection through the walls of the alveoli or the bronchi into the surrounding air spaces. Acute inflammation of the larger bronchi usually accompanies it, but is not constant. Atelectasis varying in extent is very commonly present. The same is true of emphysema. Cases of extensive confluent bronchopneumonia occur.

The systemic lesions due to the absorption of the diphtheria toxins are partly degenerative, partly exudative, and partly proliferative in

character. They are more or less characteristic, but are not specific. Some of the systemic lesions are of little clinical significance, but others, especially those occurring in the heart, the kidneys, and the nerves, are often of vital importance. The systemic lesions due to the toxins of the diphtheria bacillus are often complicated by the toxins absorbed from other bacteria which invade the primary lesions, or from those bacteria which give rise to secondary lesions in the lungs.

In the heart, so-called fatty degeneration of the *myocardium* is one of the most common lesions; it is found especially in the severe cases of short duration. It varies in extent, at times affecting the myocardium generally, at times occurring in foci. The fatty degeneration accompanies and seems to precede the other more advanced forms of degeneration which lead to the complete destruction of the muscle fibers. These more marked changes are the destruction of the sarcous elements, which become swollen, broken up, and converted into hyaline masses, and the formation within the cells of large vacuoles, which differ in size and by their irregularity in shape form the fat vacuoles. These degenerations may be so extensive as to account fully for the impairment of the heart action observed clinically. No bacteria are found in connection with these degenerative changes; they are due to the influence of the toxic substances circulating in the blood. Mural thrombi are due to the extension of the primary necrosis of the myocardium to the endocardium.

Reparative changes in these foci result in the formation of areas of sclerosis. The necrotic muscle fibers are removed through the agency of polymorphonuclear and endothelial leukocytes. The connective tissue contracts and is usually infiltrated for a long time with a certain number of lymphocytes. Occasionally foci of lymphocytes are found in the heart without any evidence of necrosis. They are properly attracted by toxins in the lymph.

Lesions of the spleen play but a slight part. Macroscopically the spleen does not differ from normal, except that the lymph nodules usually are more prominent. The most obvious lesion, microscopically, consists of the formation of foci of epithelioid cells in the lymph nodules. These cells are of the same character and are formed in the same way as those in the lymph nodes. They are phagocytic, and the nuclear detritus found in them comes chiefly from the lymphoid cells. A frequent lesion is hyaline degeneration of the walls of the arteries, which is more common in the vessels of the spleen than elsewhere.

Occasionally, as in scarlet fever, accumulations of lymphoid and plasma cells are found in the intima of veins beneath the lining endothelium. In some cases the cells are uniformly distributed; in others they form nodular projections into the lumen of the vessel.

In a few instances a diphtheritic membrane is formed in the stomach. The membrane is always attached to a surface deprived of epithelium, but may extend out some distance over apparently normal mucous membrane. Very rarely a diphtheritic membrane may be present in the duodenum. Below this point but little macroscopic change is found in the intestine beyond swelling of the lymphoid tissue, especially of the lymph nodules.

The lesions in the liver are not characteristic, they are due to the effect of soluble toxic substances and not to the presence of diphtheria bacilli. The most common lesions are a general degeneration (albuminous and fatty) of the liver cells, and more rarely necroses, limited chiefly to the centre of the lobules.

In the kidneys a variety of lesions may be found, either degenerative, exudative, or proliferative in character. The degenerative changes in the epithelium consist of cloudy swelling, the deposition of fat droplets, and the transformation of the cytoplasm into hyaline droplets.

The most common and important lesion is acute tubular nephritis. It shows necrosis of renal epithelium and an exudation of polymorphonuclear and endothelial leukocytes into the tubules, often associated with fibrin formation. The inflammatory reaction in the intertubular tissue is, however, usually much more prominent than that in the tubules, so that the name of acute interstitial non-suppurative nephritis has been applied to the condition. It often shows a marked infiltration of the connective tissue, chiefly in the cortex, with lymphoid and plasma cells. These changes in the interstitial tissue are always accompanied by the crowding of the bloodvessels, especially in the upper part of the pyramids, with the same cells which emigrate out into the tissues. In the most marked cases of this lesion the kidneys are greatly enlarged and may weigh more than four times the normal. On section the normal markings are obliterated, and the contrast between pyramids and cortex is indistinct. The increased size is due chiefly to the swelling of the cortex. Acute glomerulonephritis is much less common than the interstitial form, and the lesion is chiefly of the intracapillary type. Slight hemorrhages in the kidney occur occasionally, but hemorrhagic nephritis with escape of blood into the tubules is very rare.

The lesions in the lymph nodes are among the most constant changes and are most marked in cases of great intensity in which death takes place early. They are most marked in those lymph nodes, *e. g.*, the cervical, which are nearest the primary local process and, hence, receive the diphtheria toxins in the most concentrated form. Macroscopically the most affected lymph nodes are enlarged, soft, and hyperemic. In some cases there is extensive hemorrhage, and diffuse and circumscribed necroses are not uncommon.

In the tonsils local primary lesions of the surface with extension to the crypts are combined with the lesions of the underlying lymphoid tissue. In the thymus gland nothing is found beyond degeneration of lymphoid cells.

In the bone-marrow the chief lesion consists of a hyperplasia of plasma cells which enter the general circulation and may emigrate into various organs, more especially the kidneys, giving rise to interstitial changes. This process is not peculiar to diphtheria.

No changes have been observed in the pancreas, adrenals, thyroid and salivary glands, pituitary body, testicles, and ovaries.

In the nervous system various degrees of fatty degeneration frequently occur. The process seems to begin almost invariably in the myelin sheath.

The myelin breaks up into granules, droplets, and very irregular figures. The change in the axis-cylinder consists chiefly of swelling which is often irregular, so that it presents a beaded appearance, and as it swells it stains very faintly, so that when the myelin sheaths have undergone marked fatty degeneration, the axis-cylinders usually can not be distinguished. These changes occur not only in the peripheral nerves, but also in the white matter of the brain and cord. They are the cause of the most important sequel, paralysis.

The skeletal muscles, like the nerves, often show various degrees of fatty degeneration. In fact, the process in the two tissues seems to occur at the same time and to be of equal intensity. The muscle fibers may be affected uniformly, or only single fibers may contain fat droplets.

These degenerative changes in the nervous system and in the skeletal muscles, together with the lesions in the heart, account for the slow recovery and persistent weakness in many patients after diphtheria. Similar changes of a milder type are probably usually present.

Symptoms.—The *incubation* period is from twenty-four hours to three days. Diphtheria differs from other infectious diseases in this, as the process of infection is similar to that of a dissecting wound. The organism finds access through an abrasion in the same way as infection is produced from the prick of a needle at an autopsy.

The *onset* is usually gradual and insidious, and the subjective symptoms slight, particularly in children. Often lassitude and anorexia and headache are the only subjective signs. The child may lounge about for several days before complaining of the throat, and in severe cases the throat and neck may be markedly swollen without complaint of sore throat. Occasionally, however, the disease comes on suddenly with a high fever and markedly sore throat, headache, and toxic symptoms. In babies it may be ushered in with convulsions, which may persist for twenty-four hours, rarely longer. Vomiting occurs in a small number. The symptoms vary according to the part affected, and for convenience are described under several headings.

Pharyngeal Diphtheria.—In a typical case the throat becomes sore and there is slight or moderate fever and headache. At this time the throat shows a dull redness, sometimes an almost bluish redness, usually localized at one or both sides of the fauces. At the end of twenty-four hours patches of grayish-white membrane may be seen. In another twenty-four hours these may extend rapidly, becoming thicker, covering the tonsils, pillars, uvula, and may extend over the soft and even the hard palate. The swelling of the throat is marked and the neck begins to show a soft elastic, often only slightly tender, swelling, which is often thought to be mumps. Prostration may not be severe and the patient does not seem very ill. As the disease progresses the membrane becomes thicker, and may be removed with some difficulty, leaving a bleeding surface. In the very early stages of the membrane formation, the exudate may be removed with little difficulty and without bleeding, and failure to recognize this fact has frequently led to errors of diagnosis.

With further progress, prostration becomes evident and the patient

has an anxious, pale appearance. The pulse becomes soft and compressible. There may be apathy or moderate delirium, or at times active delirium. This is much less common in diphtheria than in other severe infections. The breath has a peculiar sweet septic odor. With extension to the nose a profuse nasal discharge of thin seropurulent or mucoid blood-streaked material appears, which excoriates the nostrils and lip.

Stridor, aphonia, and dyspnœa may appear with extension to the larynx. There may be hemorrhage from the mucous surfaces, and spots of ecchymosis appear on the skin, which is cold and clammy. The pulse is weak and rapid, the mind is dull, and if aroused the patient is confused and wandering. The urine is scanty and loaded with albumin. Nourishment is refused, partly because of dysphagia, and partly from weakness and lack of desire. Death ensues from the toxic effect on the nerve centres.

If this does not occur the membrane may exfoliate at the end of seven or eight days. The patient may steadily improve for a time and seem to be well, when suddenly, in the second week, there is vomiting, collapse, and death in a few hours. Sometimes at the end of three or four weeks when everything is progressing favorably, the pulse may fall rapidly to 30 or 40, or even lower. Then the patient, without any complaint or discomfort, gradually sinks and dies. The effect of toxin on the heart is always to be borne in mind, no matter how mild the attack A patch of membrane, the size of the thumb nail, may be attended with sufficient toxin to produce death. In case the patient passes these dangers, paralysis may still appear and produce a fatal termination through its effect on the respiratory muscles.

Temperature.—Fever in diphtheria is usually moderate. In 1000 consecutive non-fatal cases it was found that the maximum temperature in 4 cases was 105°; in 22 it was 104°; in 55 it was 103°; and in 919 it did not rise above 102° F. The temperature may drop with advancing diphtheria and even reach normal. Many of the advanced cases have a normal temperature when the physician is first called.

Pulse.—The rate is usually slightly elevated; the volume is good. In laryngeal cases the pulse is often very rapid if there is dyspnœa. As the disease advances it usually becomes soft and of low tension, due to the effect of the toxin on the vasomotor centre.

Membrane.—This appears in from six hours to three days after inflammation begins. It is thin and filmy at first, and may be readily removed without any bleeding. As it becomes thick it is more adherent, and if forcibly removed leaves bleeding-points where the vessels have been torn. It rapidly re-forms after removal. The color is typically grayish white, often translucent—the hyaline form—but it may be opaque, yellowish, brown, or even black, from coloration of drugs or extravasated decomposing blood. It has a sharply defined raised edge.

It may occur on any tissue surface, but the tonsils and pillars are most commonly involved. The uvula, soft palate, and postpharyngeal walls are frequently involved. The buccal mucous membrane and lips are less frequently involved, and the tongue rarely. Membrane may extend

from the tonsils to the lingual tonsil and down the œsophagus causing dysphagia. Surrounding the membrane there is a zone of dull red erythema which is usually less than one-half inch in diameter, and often hardly noticeable. *Œdema* of the tissues of the throat occurs in nearly all severe cases, and is very striking in some. At times the œdema precedes the formation of membrane by from one to three days, and may lead to the belief that the patient has a peritonsillar abscess.

Nervous Symptoms.—Convulsions may occur at the onset, especially in infants and young children. Delirium rarely occurs except in severe advanced cases, and usually is less active than in scarlet or typhoid fever. Mental dulness is common in severe attacks.

Gastro-enteric Symptoms.—Vomiting is much less frequent than in scarlet fever, occurring in about 10 per cent. Constipation is usually present, and diarrhœa is rare.

Laryngeal Diphtheria.—The symptoms are largely due to mechanical interference with the laryngeal functions and with breathing. It may be primary or extend from faucial or nasal diphtheria. In primary laryngeal diphtheria toxin is rarely absorbed in sufficient quantities to cause death or any of the toxic degenerations, such as paralysis. The attack begins with a hoarse, croupy cough, a moderate rise in temperature, or with no fever. The throat may be normal. In a few hours or a day the cough increases, becomes high-pitched and metallic. Dyspnœa becomes more marked, and restlessness, cyanosis, and dilatation of the alæ nasi appear. Nourishment is refused. The child resists any attention which interferes with breathing. There is marked substernal and suprasternal retraction. The sternocleidomastoids and other accessory muscles of respiration are called into play. If unrelieved the restlessness becomes less active, the cyanosis is replaced by pallor, and the child soon dies. The stridor and dyspnœa are both inspiratory and expiratory. Membrane may be present only in the larynx, or may extend throughout the trachea, the primary bronchi and even down the whole respiratory tree to the finer ramifications.

Nasal Diphtheria.—Nasal diphtheria may be severe or mild, depending on the virulence of the organism, the resistance of the patient, and the part of the nose affected. When the posterior nares and nasal vault are involved, the absorption of toxin is rapid and marked. These cases are often not recognized, because no membrane is seen, until the patient shows the circulatory disturbance of diphtheria toxemia. There is usually nasal obstruction with a nasal dischage which is serous or mucoid with slight streaks of blood. There may be marked and even fatal nasal hemorrhage. The cervical glands become swollen, and there is a marked œdema of the neck. When the anterior nares are involved alone, the symptoms are slight, and often the disease runs a prolonged course. There is a purulent nasal discharge with crusting and excoriation of the nostrils, slight or no fever and practically no general symptoms. The membrane in the nose if removed will re-form. While this form of diphtheria at times develops into more serious types, its greatest importance is as a source of spread to others. All profuse nasal discharges, especially with excoriation about the nose, should be looked upon with

suspicion and cultures taken. On swabbing out the nose and examining with a speculum in a good light the membrane may be seen. In case of operations on the nose and throat, cultures should be taken as a precautionary measure, especially if the patient gives a history of recent inflammation.

The accessory sinuses may be involved by the diphtheritic process, but the symptoms are usually slight or absent, or masked by the process in the nares. Recognition must be by transillumination and intranasal examination. Unless involved by secondary infection they usually subside with the nasal membrane. Mild forms may simply show prolonged rhinitis with crusting purulent discharge and excoriation. Such cases are often the source of epidemics.

Cutaneous Diphtheria.—Cutaneous diphtheria, as a rule, is not serious, as the membrane does not extend owing to unsuitable conditions. This does not apply to those cases where there is an abrasion such as a bite on the finger of the operator during intubation, for in these fatal results have followed. It is not an uncommon thing for a female child to carry the infection from the nose to the vulva. An attack of diphtheria of the vulva is frequently attended with marked constitutional disturbance, tenderness of the abdomen, and painful micturition. It rarely happens that toxin sufficient to cause the death of the patient is generated, although there may be a certain amount of paralysis. In male children the penis is sometimes inoculated, but this is not serious. Diphtheria of the penis in adults is frequently mistaken for a chancre and has been followed by postdiphtheritic paralysis.

In a fatal case of cutaneous diphtheria seen by the writers the infection occurred on eczema lesions and there was an extensive membrane covering the groin, lower abdomen, buttocks, and thighs. The bacillus was isolated and proved virulent. In this case there was no nasal or faucial involvement and the source was not found.[1]

Diphtheria of the *uterus* in the puerperium has been reported several times. In most cases, however, careful cultural studies have not been made and the diagnosis rests on morphology, involvement of the nose and throat, and the prevalence of the disease in its ordinary form.

Diphtheria of the Eye.—Diphtheria of the eye, or diphtheritic conjunctivitis, is not infrequent. It is sometimes caused by the secretions from the throat of the patient being coughed into the eyes of the attendant, particularly in tracheotomy cases. The more common cause is auto-inoculation from the nasal discharge. Diphtheria of the eye commences with a slight congestion, which rapidly increases and is followed by the formation of a distinct membrane which has a grayish-white appearance, a little different from that of the membrane in the throat. The process goes on very rapidly, so that at the end of twenty-four or thirty-six hours the eye is so inflamed that it is impossible to separate the eyelids. There are two varieties of diphtheria of the eye—the superficial and the deep—each of which is very serious. In the former the eye is invariably lost; in the latter it is sometimes saved. There is a

[1] *Boston Medical and Surgical Journal*, 1910, clxiii, 730.

considerable amount of constitutional disturbance and usually severe pain. The rapidity with which the disease advances is very great, so that sometimes in forty-eight hours the eye is destroyed. In the milder attacks, even when the eye is saved, the morbid process continues for six or seven days. If the attack comes on during the course of measles the probability of saving the eye is very slight.

Diphtheria of the Lungs.—This is extremely rare but does occur. The focus is situated in one of the larger subdivisions of the bronchi, and the membrane rapidly extends to the bronchioles and to the larynx. The symptoms simulate those of pneumonia, but dyspnœa is more marked and there is an absence of rusty sputum. The expectoration is mucopurulent, and cultures show the presence of diphtheria bacilli.

In some cases there are areas of occluded respiration, while the resonance remains good. When the pulmonary diphtheria is attended by faucial or nasal processes, the signs will clear up under antitoxin treatment, coincident with the throat and nose, and may be followed by a second bronchial pneumonia in the same area due to secondary infection. It is reasonable to believe that primary diphtheria of the lungs is much more common than is generally supposed.

Mixed Infection.—Diphtheria infection may occur with scarlet fever and other diseases producing throat inflammation. Secondary infection with streptococcus and other pus cocci may occur. Many believe that all the severer forms of diphtheritic infection, with marked swelling of the throat, are due to mixed infection with the streptococcus. That this is not so in most cases is evident from the uniform rapid clearing of the inflammation when large doses of antitoxin are given and the frequent development of the typical diphtheritic degenerations later. Serum would not have such an effect in streptococcus sepsis.

Complications.—*Rashes.*—In severe attacks an erythematous eruption may appear on various parts of the body, which must be distinguished from the eruption caused by antitoxin. This appears in severe attacks and is of grave import. Urticaria not connected with antitoxin sometimes appears but, although annoying, is not serious. Purpura hemorrhagica is present in the gravest types of the disease, and is generally the forerunner of death. Minute petechiæ appear on the body at first, and gradually increase in size until large spots of ecchymosis are present in the dependent portions. In some instances nearly the entire trunk may be the seat of this extravasation, only small areas of sound skin being apparent. Hemorrhage from the mucous surfaces is frequently present in severe types of the disease. There may be bleeding from the urethra and from the vagina. The hemorrhage, however, is more generally found to occur from the nose and mouth. The quantity of blood lost may be small, or so profuse as to endanger life.

Otitis Media.—Disease of the middle ear not infrequently occurs, and can be explained by the extension of the process through the Eustachian tube. Mastoiditis requiring operative interference is somewhat infrequent, but the possibility of its occurrence should always be borne in mind. It is usually of a mild and not especially destructive type and the symptoms are often obscure.

Albuminuria is practically always present in the severer cases in the acute stage. It has diminished in frequency since antitoxin was used. Albuminuria was described fifty years ago by many observers and was reported in from 55 to 70 per cent. Renal complications are not common since the use of antitoxin but are very serious. Uremia with marked convulsions appears in the graver types and there may be partial or complete suppression of urine. With complete suppression the condition, although very grave, is not necessarily fatal, for instances have been observed in which no urine was passed for forty-eight hours and the patients recovered.

Cervical adenitis is frequent and in a certain proportion ends in suppuration. Cultures show the presence of streptococci and staphylococci. Abscesses elsewhere very rarely occur and, if at the site of serum injection, are generally due to some error in sterilization. In rare instances the serum may be at fault. Septicemia, septic arthritis, and pyemia occur with diphtheria rarely. The elbow, knee, wrist, and sternoclavicular joints have been involved in our cases.

Bronchopneumonia appears during the second week in a large proportion of the cases of the laryngeal form, and is responsible for about 46 per cent. of the deaths in cases of intubation. In cases of intubation in which there was no membrane in the throat or nose, over 75 per cent. of the deaths were due to bronchopneumonia. It is especially dangerous in young children and infants. The causes of pulmonary involvement are as follows: (1) Exhaustion due to the prolonged physical work of muscles of respiration against obstruction. (2) Lack of food, and especially fluids, as the demand for air causes the patient to refuse to swallow. (3) Loss of sleep and restlessness. (4) Insufficient oxygenation. (5) Extension downward of the infection aided frequently by mucopurulent and bacterial accumulations below the stricture. Aspiration of food has been shown by Northrup not to play any part in this complication. Bronchopneumonia is much more frequent in cases of prolonged and marked obstruction than when early relief is obtained. Lobar pneumonia may commence during the second week, but is not nearly so frequent as bronchopneumonia.

Paralysis of a mild or severe type is one of the most frequent of the sequelæ and occurs in about 40 per cent. of all attacks of the disease. Some observers have given a much lower percentage, but this is due to the fact that the slight attacks have not been recognized. The patellar reflexes are absent in a very large proportion of all cases, even when paralysis is not so marked as to attract attention.

Postdiphtheritic paralysis is due to degeneration of the nerve fibers from the action of the toxin. It occurs most frequently at the part involved by the membrane, as the fauces, and when this is unilateral, the most marked paralysis is on that side of the throat. This local paralysis is apparently due to the action of the toxin locally during absorption, as well as from the effect of that absorbed by the bloodstream. Faucial paralysis is characterized by nasal voice, inequality of motion of the palate, and nasal regurgitation. There is often marked loss of sensation in the throat. When the pharyngeal constrictors are

paralyzed there is dysphagia. Mucus often collects in the throat, and the peculiar hollow, rattling, and ineffective cough is very characteristic. Oftentimes the diagnosis of diphtheria is first made when the patient is first seen for palatal paralysis, or paralysis of other parts. Paralysis of the extrinsic and intrinsic muscles of the eye is common, and is associated with double vision and not infrequently dilated pupils, which react to light more or less. There is inability to read because of loss of power of accommodation.

The skeletal muscles of the upper and lower extremities may be involved, usually in the third to the sixth week of convalescence, so that the patient is unable to use hands or legs. The respiratory muscles are sometimes paralyzed and the patient has a shallow sighing respiration. This has been observed in about 3 per cent. of the fatal cases at the South Department in the past nine years. Laryngeal paralysis occurs chiefly with the faucial and nasal toxic forms. Evidence of laryngeal paralysis due to laryngeal diphtheria is rare, although postdiphtheritic laryngeal obstruction is not infrequently ascribed to this cause. Laryngeal paralysis is usually attended by partial or complete aphonia. Facial paralysis is rare.

The onset of paralysis occurs from the end of the first to the sixth or eighth week. It often occurs first at one part, as the throat, and then appears successively in the eyes, the larynx, hands, feet, and neck, clearing in the same order. It may be still advancing after six or eight weeks. The paralysis is never permanent, although such has at times been reported. Permanent paralysis has been seen in our wards only when due to coincident disease of the central nervous system, as thrombosis or embolism, and acute poliomyelitis.

Sensory paralysis is less marked than motor, and often does not accompany the motor forms. It is marked in the severe cases, at times showing often a loss of the pain sense while retaining the touch perception. Loss of muscle sense is occasionally present, and ataxia is marked for a time. Smooth muscle is apparently never affected, and loss of sphincter control is very rare.

In a certain number of cases four or five weeks after the initial symptoms a multiple neuritis appears, with severe pain and loss of motion of the extremities. This is grave and a frequent cause of death.

Heart.—The gravest sequel, and one that is responsible for the greatest number of deaths occurring in apparent convalescence, is the effect of the toxin on the heart. In every case of diphtheria, mild or severe, the possibility of heart complications should always be in the mind of the physician, and frequent examinations should be a routine, no matter whether there are any symptoms referable to this organ or not. The heart complications are a phase of the degenerative changes in the nervous system, although in some of the fatal cases a degenerative change in the heart muscle has been found. Murmurs, usually systolic, are observed in the vast majority of patients with diphtheria. Vomiting may draw attention to a cardiac complication. Before this symptom there is usually a softening of the first sound and shortening of the diastolic pause. Pallor and restlessness are very early and grave symp-

toms. There is no œdema and cyanosis is uncommon. The heart may or may not show dilatation, but gallop rhythm or signs of heart-block are present. The pulse may remain normal, but more often is rapid. When a sudden drop in the pulse occurs, the condition is very serious.

In the observation of the pulse-rate of 800 cases of diphtheria the following results were reached: When the rate was less than 130 the mortality was 4.8 per cent.; when it was 130 the mortality was 16.2 per cent.; when 140 the mortality was 18.2 per cent.; when 150 the mortality was 40 per cent.; when 160 the mortality was 56.1 per cent.; when 170 there was a death-rate of 75 per cent.; and when the pulse-rate was 180, the mortality was 90.9 per cent.

The conclusions reached by White and Smith[1] in the clinical study of 946 cases of diphtheria with reference to heart complications are of interest, the special points being:

"1. The great frequency of heart murmurs and irregularity of the pulse. The prognosis does not depend on the mere presence of these signs, but upon the severity of the infection, the length of time without treatment, the rate and degree of irregularity of the pulse, and the presence of the graver signs of cardiac disturbance. (2) Moderate disturbance of the heart is very common; severe complications are infrequent. (3) Frequent examinations of the heart are necessary to really determine its condition, because of the marked changes in rhythm from one hour to the next. (4) Gallop rhythm, late vomiting, and epigastric pain and tenderness, are important as danger signals of severe heart complications. The association of late vomiting with gallop rhythm renders the outlook almost hopeless. (5) Antitoxin does not affect the heart unfavorably, but, on the other hand, its early use prevents the appearance of grave heart complication. (6) Bronchopneumonia is a more frequent fatal complication of diphtheria than heart disease; sudden death from heart disease is very rare when patients are kept in bed for a proper period. (7) Prolonged rest in bed is necessary in all severe cases; it is not necessary to keep all patients in bed who have cardiac murmurs and a pulse which is somewhat irregular and increased in rate. One should be governed by the stage of the illness and the general condition. If no serious heart trouble has developed within four weeks, the patients are usually safe from this complication. (8) Heart murmurs and irregularity are of long duration in many cases and make it necessary to watch the condition of the heart long after convalescence in all severe cases."

Vomiting is, as a rule, an indication of commencing degeneration of the vagus nerve. There is no one symptom that should cause so much alarm in the convalescent stage of diphtheria as a sudden unexplained attack of vomiting. Very few patients in this condition recover. This degeneration of the vagus does not seem to be sufficiently appreciated by the profession at large. The possibility of its occurrence during the convalescent stage of a comparatively mild attack cannot be too strongly emphasized. Vomiting may be associated with urticaria, and as this

[1] *Medical Communications of Massachusetts Medical Society*, 1904.

occurs at about the time heart complications often appear in the second week, great care should be used to determine whether the vomiting is the result of the serum or toxic degeneration.

Thomas,[1] from the study of 25 cases, describes the changes in the nervous system produced by diphtheria as: (1) A marked parenchymatous degeneration of the peripheral nerves, sometimes accompanied by an interstitial process, and hyperemia and hemorrhages; (2) acute diffuse parenchymatous degenerations of the nerve fibers of the cord and brain; (3) no changes, or but slight ones, in the nerve cells; (4) acute parenchymatous and interstitial changes in the muscles, especially the heart muscle; (5) occasional hyperemia, or infiltration, or hemorrhage in the brain or cord, in rare cases severe enough to produce permanent changes, such as the cases of multiple sclerosis and of hemiplegia which have been observed.

Diagnosis.—This is based on the presence of the dull red inflammation, œdema, membrane and discharge, as well as the special symptoms due to the local interference with function, as in the larynx. In typical cases this picture is not likely to be mistaken, but the variation is so great, and the similarity of other inflammations so marked, that the diagnosis may be very difficult. The temperature and pulse afford little aid, although a low temperature and pulse-rate are more characteristic.

Tonsillitis may be mistaken for diphtheria, especially when the small follicular patches run together. The subjective symptoms are usually more severe, the temperature higher, and pains in the back and extremities are more marked than in diphtheria. The exudate usually wipes off easily. Diphtheria may begin as the follicular process, however, and this should be kept in mind and cultures taken in all cases.

"*Streptococcus Throat.*"—Extensive membrane may occur in this infection, which may be indistinguishable from diphtheria except culturally. The membrane is often less thick and more poorly defined, and of a more intense white. It may wipe off easily or be firmly attached. The most characteristic difference from diphtheria is the intense bright injection which usually extends over a large zone from the membrane.

Syphilis.—Primary syphilis of the tonsils and secondary and tertiary lesions of the mucous membrane may be confused with diphtheria. In chancre of the tonsils, the slow process, the hard infiltration, the primary adenopathy serve to differentiate. In the late lesions the destructive effects on the tissues, ulceration, the multiple involvement, especially of the gums and lips, the slower course, the skin lesions and general adenopathy, usually make the diagnosis clear. Redness may be marked in syphilis. A symmetrical distribution is common in both. The Wassermann reaction and the luetin test may aid.

Vincent's Angina.—This is very frequently diagnosed as diphtheria, chiefly because the disease is so little known. The shallow, sharp-cut ulceration filled with cheesy, white, grayish or greenish friable membrane with a very foul odor, showing enormous numbers of

[1] *Medical and Surgical Reports, Boston City Hospital,* Ninth Series, 1898, p. 83.

B. fusiformis and spirochetes in smears is very characteristic. The process is more chronic and often causes the patient little pain or disturbance. The exudate in some cases obscures the ulcer but a swab will detect this by sinking into the cheesy material.

Peritonsillar Abcess.—Many instances have occurred in which the acute œdema of diphtheria has been mistaken for peritonsillar abscess. The incision yields no pus, the swelling rapidly increases, and unless antitoxin is given, death may follow. In diphtheria, there is less difficulty in opening the mouth, the injection is of a more bluish color and the subjective symptoms usually less severe. In doubtful cases cultures should be taken before operation.

Mercurial stomatitis may simulate diphtheria because of the gray membranous-like necrosis. Its slow course, the frequent involvement of the gums, the loose teeth and the relatively slight local reaction differentiate. Acute poisoning with corrosive sublimate, ammonia, zinc chloride, etc., may give gray patches which are as a rule easily differentiated by location, extent and type.

Scarlet fever often has an extensive membrane closely simulating diphtheria and, in fact, is not rarely diagnosed diphtheria. Most false membranes in scarlet fever are due to the streptococcus, but diphtheria may be associated and cultures are essential to correct diagnosis.

Thrush involving the tonsil may be recognized by the white raised fungoid appearance, especially as it involves the buccal membrane.

Postoperative ulcerations may cause some difficulty. The surrounding reaction and the raised exudate in diphtheria are usually different. In diphtheria following such operations it is often very difficult to make a diagnosis. Exudates which occur in dirty mouths in febrile diseases, especially with mouth breathing, are at times mistaken for diphtheria. These have no real connection with the mucous membrane, being simply deposited on the surface, and when removed present no evidence of fibrinous structure.

Nasal diphtheria must always be considered in acute nasal obstructions, especially with sero-muco-purulent discharge excoriating the nostrils. The membrane may be difficult to see and cultures should always be taken. Foreign bodies and occasionally streptococcus and staphylococcus infections may simulate it. Crusts in acute infections and ozena may look like diphtheria at times.

Laryngeal diphtheria is diagnosed by the croupy cough, stridor, interference with voice production, dyspnœa, and its effects. When not attended by involvement of the nose and throat no other signs are present. Laryngeal examination with the laryngoscope is of great help. In nervous and young children this is often difficult, and the direct method with a laryngeal speculum is necessary. The urgent dyspnœa often makes any method of examination impracticable unless the examiner possesses considerable skill. Other acute infections of the larynx producing obstruction and exudate cannot always be differentiated, but they usually occur secondary to acute diseases.

Spasmodic Croup.—A sudden onset in the absence of aphonia or hoarseness and especially sudden subsidence serve to differentiate this.

Examination of the larynx shows adduction of the cords, but no membrane or œdema.

Subglottic Œdema.—This when due to other infection than the Klebs-Loeffler bacillus may give the symptoms of laryngeal diphtheria. The examination of the larynx is required to differentiate.

Phlegmon of the Glottis.—The dyspnœa occurring in this condition may suggest laryngeal diphtheria. There is, however, no aphonia, or croupy cough, and inspiratory dyspnœa is usually more marked than expiratory. Examination shows a marked swelling of the epiglottis and arytenoid region.

Retropharyngeal Abscess.—In small children, particularly, this leads to the diagnosis of laryngeal diphtheria. The absence of aphonia and croupy cough, the muffled voice, the dysphagia, greater inspiratory dyspnœa, the higher pitched more "throaty" stridor, the increase of dyspnœa on opening the mouth or extending the head, are suggestive, and the exploring finger detects the boggy fluctuating swelling on the postpharyngeal wall. Visual examination often shows very little, and the value of digital examination cannot be overestimated.

Foreign Bodies.—Peas, beans, pins, fishbones, peanuts, etc., may be drawn into the larynx and trachea of children and lead to the belief that the obstruction is due to disease. When the obstruction is below the larynx, the expiratory dyspnœa is usually greater than inspiratory. There may be paroxysmal obstruction due to ball valve action.

Nervous Diseases.—In certain of the acute affections of the nervous system, such as basilar meningitis and acute poliomyelitis, there may be laryngeal symptoms due to irritation of the bulb and basal ganglia.

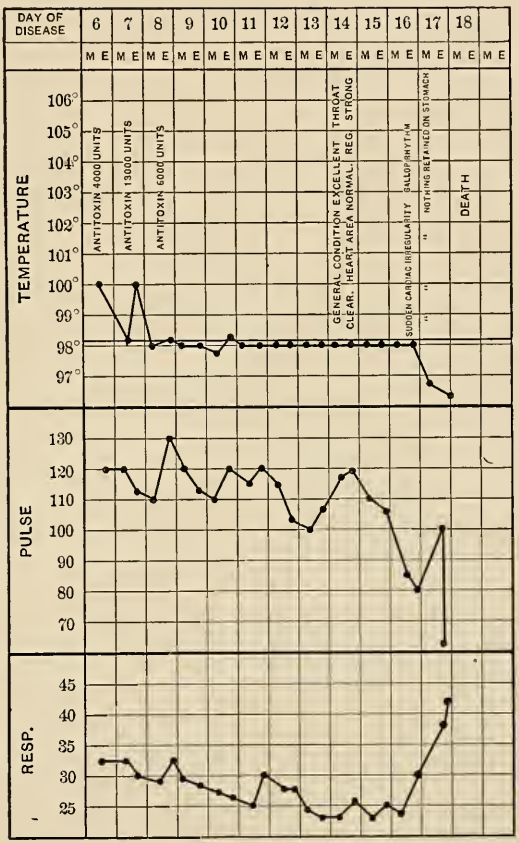
Recurrent laryngeal nerve paralysis, thymic asthma, mediastinal tumors, and peritracheal glands and peritracheal abscess, cause suspicion of laryngeal diphtheria at times. In these conditions, the obstruction is below the larynx and there is no loss of laryngeal function. The expiratory dyspnœa exceeds the inspiratory, as a rule, and percussion, *x*-rays, and the course may clear the diagnosis.

Pulmonary Diphtheria.—Pulmonary diphtheria unless associated with laryngeal, pharyngeal, and nasal involvement, is not usually discovered unless the patient coughs up membrane. Lung involvement with little fever and slight dulness, especially if the signs are those of occluded areas with few signs of consolidation, should always be suspected as diphtheria. In the vast majority of cases the process starts in the larynx and trachea. Non-diphtheritic membranous bronchitis may be impossible to separate from diphtheria of the lungs, and should always be considered as diphtheritic until that can be excluded by culture study.

The early acute laryngeal infection occurring in measles, may lead to diagnosis of laryngeal diphtheria. The Koplik spots and catarrhal symptoms should make the measles clear. Diphtheria may, however, occur with any other disease, especially measles and many of the severe diphtheria cases, particularly of the larynx, are complications of this disease. It occurs also with typhoid fever, pneumonia, during the later stages of pulmonary tuberculosis, and with scarlet fever.

The importance of a *bacteriological* examination in all cases of suspicious sore throat cannot be overestimated. Much has been said about the inaccuracy of cultural diagnosis, and while mistakes may be made in the laboratory, the chances of error are very much less in cultural diagnosis than in the clinical. One great source of error is carelessness in taking the culture. The swab is simply put into the mouth and does not come in contact with the membrane. The swab should be

FIG. 13


DAY OF DISEASE
6 7 8 9 10 11 12 13 14 15 16 17 18
M E M E M E M E M E M E M E M E M E M E M E M E M E M E
TEMPERATURE
106° 105° 104° 103° 102° 101° 100° 99° 98° 97°
ANTITOXIN 4000 UNITS
ANTITOXIN 13000 UNITS
ANTITOXIN 6000 UNITS
GENERAL CONDITION EXCELLENT THROAT CLEAR. HEART AREA NORMAL. REG. STRONG
SUDDEN CARDIAC IRREGULARITY GALLOP RHYTHM
NOTHING RETAINED ON STOMACH
DEATH
PULSE
130 120 110 100 90 80 70
RESP.
45 40 35 30 25

The temperature chart and pulse-rate in a fatal attack of diphtheria.

rubbed near the edge of the diphtheritic membrane and not over the centre of the patch. Sometimes the swab is not rubbed sufficiently on the surface of the culture medium, and consequently there is no growth. These may seem trivial matters, but it is well before criticising the work of the laboratory to be sure that the critic himself is not at fault. The reaction of the culture medium is sometimes the cause of a mistake, as the serum may be acid or very strongly alkaline. Sometimes the serum is perfectly dry, and when in this condition the

growth is disappointing, as a certain amount of moisture is necessary. To sum up the whole matter in a few words: It can be said that, in a given case, if the culture medium is of the proper reaction, if there is a sufficient amount of moisture, if the culture is taken with care, and the tube placed in the thermostat within a short time after it has been inoculated, and allowed to remain there for at least eighteen hours, the results will be satisfactory. The examination of smears from an exudate in the throat are not very satisfactory. Many instances occur where a smear gives a negative result and a culture a positive one. It is therefore well not to place too much dependence upon an examination of a smear. If a culture is examined after it has been in the incubator only six hours a positive report can be accepted, but a negative one should not be.

Some few years ago the writer made an examination of 500 throats in which the clinical diagnosis was doubtful, but there was a suspicion of diphtheria. It was found that about 40 per cent. of the cultures contained diphtheria bacilli. A diagnosis of diphtheria in these cases would not have been possible without the aid of cultures. It was also noticed that, in many instances, a positive culture was obtained twenty-four to forty-eight hours before any membrane appeared. The most common organism found with the diphtheria bacillus was the *Staphylococcus pyogenes aureus*. The *Streptococcus pyogenes* was also found.

In laryngeal diphtheria cultures are frequently of no avail because the membrane is situated so far down that it is impossible to reach it with the swab, and, therefore, the diagnosis must be made from the clinical symptoms. If the patient is intubed, or if tracheotomy is done, cultures from the intubation tube or from the tracheotomy tube show the presence of the bacilli of diphtheria. In an analysis of 1500 intubations it has been found that positive cultures were obtained in only about 60 per cent.

There are chances of error in the cultural diagnosis, for the bacteriologist is no more likely to be infallible than the clinician. They must work together. Too much has been said about laboratory diphtheria and clinical diphtheria, and the tendency has been to throw too much discredit upon the work of the bacteriologist. It is the duty of the physician to either examine cultures or have them examined in every case of suspicious sore throat, just as it is his duty to examine the urine in every case of acute disease. No antiseptic gargle or lozenge should be used for at least two hours before a culture is taken.

The statement has been made that the bacillus of diphtheria is frequently found in cultures from the throats of healthy individuals who have not been exposed to diphtheria. Loeffler found this organism 4 times in the examination of cultures from 160 well children. Park and Beebe found it in 8 out of 330, and Kober 5 times in cultures from 600 individuals. The writer examined 130 throats with this point in view, and in no instance was an organism found that gave the same staining reaction as the bacillus of diphtheria. In a few instances bacilli were found having morphologically a marked resemblance to the organism of diphtheria, but the differentiation was easily made by the staining

and cultural peculiarities. The statement has been made that the bacillus of diphtheria is frequently found in the throats of perfectly well persons who have the care of patients ill with diphtheria. The writers' experience is the opposite of this. Cultures were taken from the throats of sixty nurses on duty in the diphtheria wards of the South Department of the Boston City Hospital, and in no instance was the bacillus of diphtheria found.

Previous to the discovery of the bacillus the question of the release from isolation of a diphtheria patient was a very difficult one to decide. By cultural examination the physician is now able with certainty to say that the patient is free from infection. Two, or better more, negative cultures from the throat and nose should always be required. In certain rare instances the bacillus may remain in the throat for a very long time, but in these the organism as a rule is non-virulent and the inoculation of guinea-pigs will definitely settle the question of virulence. As a matter of fact a cultural examination shortens rather than lengthens the period of isolation. Whether the incidence of "return cases" is lessened is a matter of inquiry. So far as "return cases" of diphtheria are concerned, it may be said that they are of such rare occurrence at the South Department of the Boston City Hospital as to prove the very great importance of cultures for discharge, as in no other way can it be definitely shown that the individual is free from infection. Cultures for discharge should be commenced seven days after the disappearance of the membrane and the cessation of the discharge from the nose. It is a waste of time and labor to take cultures any earlier, and if the condition of the patient is satisfactory it is unnecessary to wait any longer.

In the larger cities, Boards of Health have established laboratories for examining cultures. In the country the physician must depend upon himself. The apparatus required is a microscope with an oil immersion lens, as incubator and culture tubes. The best culture medium is Loeffler's blood serum, but, as it is difficult to obtain the blood, egg albumen or agar-agar with Loeffler's bouillon can be substituted. The egg albumen is solidified in a coagulator, and then sterilized in the usual way. When it is necessary to have an immediate culture, an egg can be boiled for four minutes and the shell chipped off. The egg is then placed in a deep glass and the ordinary cotton plug is inserted. The exposed surface of the egg can be inoculated with the ordinary swab and placed in the incubator. Satisfactory results can be obtained in this way.

Prognosis.—This is markedly influenced by the efficiency and promptness of antitoxin treatment. In no case promptly treated by sufficient antitoxin should death occur. The effect of antitoxin is especially seen in laryngeal cases in which its early administration prevents the formation of membrane and œdema with the attending obstruction. When obstruction has occurred to a well-marked extent, the best of treatment still gives a high mortality.

With extensive membrane and œdema, especially if the neck is involved, the prognosis is always grave. When the membrane forms rapidly, the prognosis is obviously serious. Extreme age and infancy offer graver conditions, especially in the laryngeal form.

Delirium is a very unfavorable sign, and hemorrhages from the mucous membrane are very unfavorable. Ecchymosis of the skin usually means a fatal termination. Vomiting, unless due to urticaria, is always a serious sign in the early convalescence. The development of gallop rhythm or slow pulse is extremely alarming, and if attended by marked pallor and restlessness practically always fatal. About 50 to 75 per cent. of the cases with gallop rhythm die.

Pneumonia, especially in laryngeal intubed cases, is very unfavorable, averaging about 70 per cent. mortality.

Paralysis, unless it involves the respiration, is usually not serious in itself, but it always suggests the possibility of heart involvement as well. The pharyngeal paralysis may interfere with swallowing, and with a weak heart cause danger of pneumonia.

Nephritis, if severe, must always be considered a serious indication, and daily examinations of the urine should be made, not only to detect the presence of albumin and casts, but also to determine the quantity of urea eliminated. There is always a certain amount of albuminuria in diphtheria, but death from nephritis is not of very frequent occurrence.

Empyema, although it rarely occurs, is a sufficient reason for an unfavorable prognosis.

Prophylaxis.—As diphtheria is an infectious disease, in order to diminish its prevalence, it is important that infected individuals should be isolated. The room should be stripped of all hangings. The carpet and all furniture not absolutely required should be removed. Although the danger of the germs being carried by *fomites* is not so great as in some other infectious diseases, these precautions should always be taken, for the smaller the number of things to be disinfected, the less the danger of inefficient disinfection.

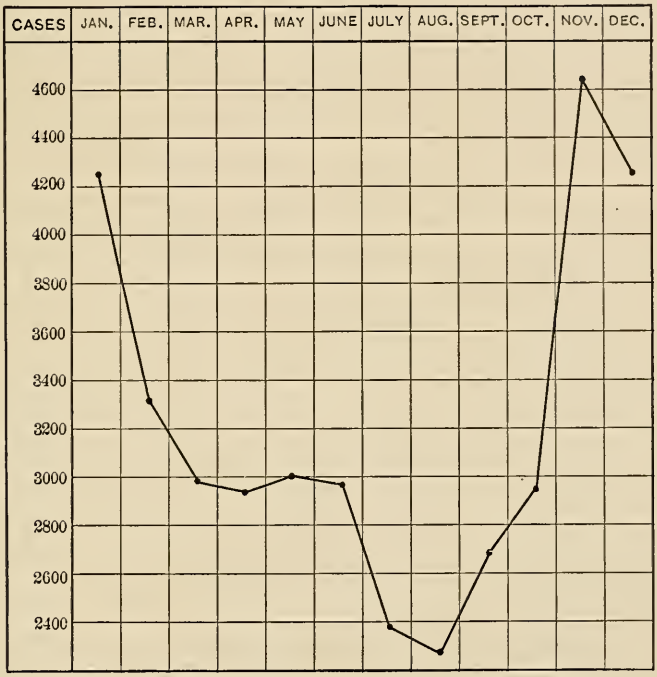
The area of infection is comparatively small, and therefore a patient can be sufficiently isolated in a house occupied by one family. The great danger of infection arises not from the patients who are seriously ill, but from the mild and unrecognized attacks, principally of the nasal type. The effect of these mild cases in increasing the prevalence, particularly in the pubic schools where children are brought in close contact, is manifest (Fig. 14). It will be seen that during the months of July and August, when the schools were not be session, the number of cases reported was very considerably less than during term time. The spread by *carriers* is an important factor. Very few figures are available as to the real danger of carriers who have not had the disease or been in close contact with it. Most of such cases harbor probably non-virulent organisms and experience seems to show that from persons with entirely normal mucous membrane, we have little to fear as carriers. It is to persons with slight nasal discharge, chronic or subacute pharyngitis and allied conditions, with the diphtheria bacilli present, that most attention must be given.

The affect of climatic conditions is not very clear. Sudden changes of temperature and strong winds with the sharp particles of dust probaby increase the susceptibility by reducing the local resistance of the mucous membrane. The close crowding in winter in dense centres of population

and the lack of personal hygiene are of importance. Epidemics due to infected milk are wellknown, and probably the milk is usually infected from human sources in handling. Dean and Todd found virulent diphtheria bacilli in sores on the teats of cows whose milk had produced a small epidemic.

Disinfection of the clothing and bed-linen is important, and, although this can be done with corrosive sublimate and boiling at the home of the patient, it could be much more satisfactorily performed if municipalities would establish sanitary wash-houses and disinfecting stations to which the infected articles could be sent. Disinfection of the room after recovery is a difficult problem, particularly in a tenement house.

FIG. 14



Cases of diphtheria in Boston, Mass., by months, from 1890 to 1904, inclusive.

If possible, the walls and floor of an infected room should be washed with corrosive sublimate. If the walls are papered, they can be rubbed with bread, the soft part of the bread acting like the bristles of a brush and the crust as the handle. It is preferable, however, to remove the paper and repaper and repaint the room. Formaldehyde in a gaseous form, if generated in sufficient quantity and if the room is tightly sealed is an effectual mode of disinfection. If there is any clothing in the room to be disinfected by formaldehyde, it must be loosely hung on the back of chairs or on suitable racks. The conclusion reached by the majority of investigators is that formaldehyde is a most powerful and practical disinfectant for large air spaces, but that it has no penetrating

power. It is important that a sufficient amount of the gas should be generated, and it is equally important that the room should be very tightly sealed. The neglect of carefully doing this is responsible for the failure in this method of disinfection. The temperature of the room has a marked influence on effectiveness, warm rooms giving much better results. The amount of moisture also effects results, and penetration is much greater if there is considerable moisture in the air.

There are many different apparatuses for generating formaldehyde; some are expensive, others quite cheap; some are effectual and others are useless. The Trillat autoclave is a very good apparatus. Lentz's generator is very useful. Schering's paraform lamp is perhaps as good an apparatus as can be used. The simplest, and also an effectual, method of generating formaldehyde consists of mixing potassium permanganate with a 40 per cent. solution of formalin. The potassium permanganate should be the commercial and not the chemically pure. No special apparatus is required. An ordinary tin dish with flaring sides can be used. The quantity of permanganate for each pint of formalin is six and one-half ounces. It is very important that the permanganate be put into the dish first, and then the formalin solution poured over it. As soon as the formalin is placed in the receptacle, a rapid exit must be made, because the gas is generated very quickly. The room should remain closed for twenty-four hours and then be thoroughly aired. The quantity of the 40 per cent. solution of formalin and of the potassium permanganate to disinfect 500 cubic feet of space is one pint of the former and six and one-half ounces of the latter.

Steam under pressure is the best method of disinfecting mattresses and woollen material. Sunlight is one of the most efficient disinfectants. Experiments have shown conclusively that many of the pathogenic microörganisms are destroyed by exposure to the direct rays of the sun for two or three days. It is, therefore, evident that in the country, where the necessary apparatus for disinfection is not obtainable, much can be accomplished by the direct exposure of the clothing of the patient to sunlight. Disinfection can never take the place of cleanliness, fresh air, and sunlight, a fact not fully appreciated by the public.

Animal Diphtheria.—Many instances have occurred where animals, especially cats and dogs, have been considered to have spread diphtheria. Cobbett reported a case of diphtheria in a horse from which virulent diphtheria bacilli producing diphtheria toxin were isolated. A child in contact had developed diphtheria.

Most of the instances of natural diphtheria in animals have lacked demonstration of the presence of true diphtheria bacilli. It is not improbable from experimental work that at times animals may contract diphtheria and be the cause of spread, but there is not sufficient evidence that this does occur. Avian diphtheria is due to an entirely different organism so far as the evidence goes.

Personal Prophylaxis.—The physician and nurse who have charge of diphtheria patients should be careful regarding the patient coughing into their faces. In tracheotomy cases, while dressing the wound, or cleaning the tube, it is well to wear glasses. All abrasions on the hands

should be carefully protected. Careful washing and disinfection of the hands should be practised and care taken that neither infected hands nor other infected objects be brought in contact with the mucous membranes. Cloths used for handkerchiefs should be immediately burned or placed in a sterilizing solution. It is not advisable to wear a gauze muzzle, because the area of infection of diphtheria is slight, the medium of communication being the discharge from the nose and mouth. The writer made an investigation on this point and found that the dust in diphtheria wards did not contain diphtheria bacilli. To demonstrate that diphtheria is not an air-borne disease, flasks of bouillon through which the air of the diphtheria wards was pumped for an hour were used, but no diphtheria bacilli were detected. Flies are not the carriers of infection, as has been demonstrated by experiments by the writer.

Treatment.—General.—Attention should be given to the hygienic surroundings, and fresh air and sunlight are important aids. Allusion has already been made to the importance of isolation. The physician in making his visits should wear a gown, and should be careful to wash his hands in a solution of corrosive sublimate after having seen the patient.

The diet during the acute stage should be liquid—milk and broths. Milk, however, is the most satisfactory and should be given in sufficient quantities at least every four hours, and oftener if desired. If there is nausea, peptonized milk or lime water and milk can be used. If no food can be retained, rectal enemata consisting of milk and egg can be used. Feeding every fifteen minutes is always to be avoided in diphtheria. The patient must not be annoyed by injudicious attempts to induce him to take food and stimulants at short intervals. Ice-cream is frequently very grateful and can be given in unlimited quantities. Alcohol in the severer cases is of much benefit, and whisky or brandy can be given in as large doses as the stomach will bear. A moderate dose may be administered at first, and gradually increased. It is surprising the amount of alcohol that a patient ill with septic diphtheria will take with positive benefit. Champagne, as a rule, is not well borne but in exceptional cases may be given with benefit. Digitalis in doses proportioned to the age is sometimes of benefit at the commencement, but in the later stages is much more likely to do harm than good, particularly when there is beginning degeneration of the heart muscle or cardiac nerves. The bowels should be kept open by mild cathartics, and the best agent is calomel in small and frequently repeated doses. Diuretics, if there is albuminuria, are to be avoided, but it is well to give a considerable quantity of water if there is no nausea. Corrosive sublimate in very small doses sometimes is of benefit, but it should be given with the utmost care. It is well to commence with $\frac{1}{60}$ of a grain for a child five years old and proportionate doses for younger children. Jacobi speaks very highly of this mode of treatment, and it certainly is of advantage in some cases. Antipyretics should not be given, for not only are they injurious to the patient, but there is no special reason for their use, as the temperature in diphtheria, except in rare instances, is not specially elevated. Tincture of chloride of iron is advised, but

the advantage derived from its use is problematical. Sometimes, when the patient is violently delirious, a small dose of morphine may have a quieting effect, but this drug should always be given with the utmost caution. Strychnine is a most useful stimulant and can be administered to very young children in proper doses with great advantage. When there is a collection of mucus in the intubation-tube, atropine can be given with seeming benefit, but a second dose should not be given until the effect of the first has passed off.

In septic cases with marked circulatory failure the injection of a pint of normal salt solution is frequently of great use. The writer has seen instances of recovery of apparently moribund patients after this treatment. It is important that the patient should remain in bed for a considerable time, even after apparent convalescence is established. This must be emphasized for the grave danger of heart complications when convalescence is apparently progressing normally, is always to be kept in mind. In severe cases rest in bed should not be less than six weeks and it is often necessary to see that the patient does not even raise the head from the pillow. The need of prolonged rest must be determined by the severity of the attack and the promptness of treatment.

Local Treatment.—Any local application that causes pain to the patient is positively harmful. All that can be done is to cleanse the mouth in the easiest way possible without exhausting the strength of the child. Loeffler's solution (menthol, 10 grams, dissolved in toluol to 36 cc. liq. ferri sesquichlorati 4 cc., and absolute alcohol 60 cc.) is a very good application. It can be used with a swab of absorbent cotton, and does not cause irritation. Irrigation with corrosive sublimate 1 to 2000 is often of use. Boracic acid irrigation frequently gives relief; irrigation with normal salt solution cleanses the mouth and removes all detached pieces of membrane. Irrigation is done by turning the child on the side and introducing the nozzle of a fountain syringe, the force of the stream being regulated by the elevation of the bag. Children will not use gargles and are frightened by sprays, but very soon become accustomed to irrigation and submit to it without struggling. Peroxide of hydrogen has been used to a very great extent. It is doubtful how much good has been accomplished by it. Dobell's solution either as a spray or as a gargle sometimes seems to be of benefit. If dysphagia is marked, painting the fauces with a 1 to 2 per cent. solution of cocaine will frequently give relief, but it has no effect on the diphtheritic membrane. When there is profuse discharge from the nose the nostrils should be thoroughly cleansed with a swab wet with some mild antiseptic solution, and then calomel insufflated. The nasal douche is to be avoided on account of the danger of its causing middle ear disease.

There is very great doubt that any degree of control of the diphtheritic process is secured by any local application. The need of local application, so strongly suggested before antitoxin treatment, has been removed by the fact that such marvellous uniform clearing of the local inflammation occurs when sufficient antitoxin alone has been used. While cleanliness is valuable, too much is often attempted in washing out the throat every one or two hours. At the suggestion of the

writers the value of this was tested by B. L. Armes and E. M. Wade at the Boston Bacteriological Laboratory of the Health Department. Washings in sterile salt solution from the throats of a series of untreated diphtheria cases with profuse discharges were at once filtered through Berkefeld filters and injected into guinea-pigs. The pigs suffered no harmful results whatever. It is evident that if insufficient toxin was present in these extreme cases, the swallowing of toxin, even granting its absorption when so swallowed, would be of no importance in the average case.

Cervical adenitis is very frequently relieved by the application of ice. Sometimes, particularly with children, warm applications are more grateful. If suppuration takes place, early incision is imperative. In rare instances pus may burrow under the deep cervical fascia and deep incisions may be required, but this is the exception. A bulging of the membrana tympani demands paracentesis in about 4 per cent. of all cases. A mastoiditis requires prompt operative interference. Because the patient has diphtheria is no reason why the operation should be postponed. Inflammation of the mastoid cells is of rare occurrence, but the probability of this complication must be borne in mind.

The treatment of postdiphtheritic paralysis must be expectant. Electricity does not do any good. Strychnine and iron as general tonics are useful, but the important things in the treatment of this sequel are rest in bed and nourishing diet. If the palatal paralysis is so marked as to interfere to any great extent with deglutition, resort must be had to œsophageal feeding.

Antitoxin Treatment.—Since the discovery of antitoxin by Behring in 1890, the mortality has undergone a very marked change. Roux stated that in certain hospitals where the death-rate had been 58 per cent. before antitoxin, since its advent it has fallen to 20 per cent. Bayeux states that of 230,000 cases reported from all parts of the world, the death-rate before antitoxin was 55 per cent. and since its use 16 per cent.

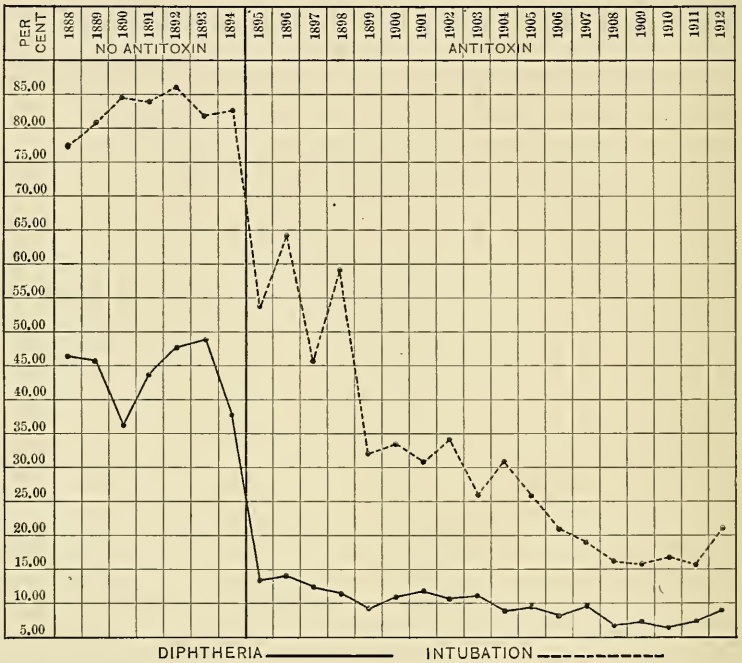
At the Boston City Hospital, from 1888 to 1894 inclusive, among 3067 cases before antitoxin the death-rate was 43.2 per cent., among 24,378 cases since antitoxin was used the mortality was 10.23 per cent., and among 6080 cases in the past five years it has been 7.8 per cent.

In the laryngeal type, of the cases intubed, the mortality before antitoxin varied from 78 to 86 per cent., averaging 82.49 per cent. Since antitoxin has been used the mortality has varied from 64.7 per cent. to 15.5 per cent., averaging 31.2 per cent. For the past five years it has averaged 18 per cent. Even this does not show the great value of antitoxin, as a very small proportion of the cases escaped operation before antitoxin, while today over 50 per cent. of the laryngeal cases in the hospital escape, and if antitoxin was given earlier and in larger amounts the number who escape operation would be much larger. In the annual report of the Metropolitan Asylums Board of London for 1903, it is stated that at the eleven hospitals under the jurisdiction of this Board, where 4839 patients were treated with antitoxin, the death-rate from diphtheria was 10.18 per cent.

In order to derive the greatest possible advantage from antitoxin it

should be given at the earliest possible moment in the course of the disease, even before the membrane has commenced to form. It is at this time, when there is a certain amount of congestion of the mucous membrane of the throat that a bacteriological examination is of great use, because almost invariably at this stage a positive culture will be obtained. If antitoxin is given at once, it will prevent the formation of membrane.

Fig. 15

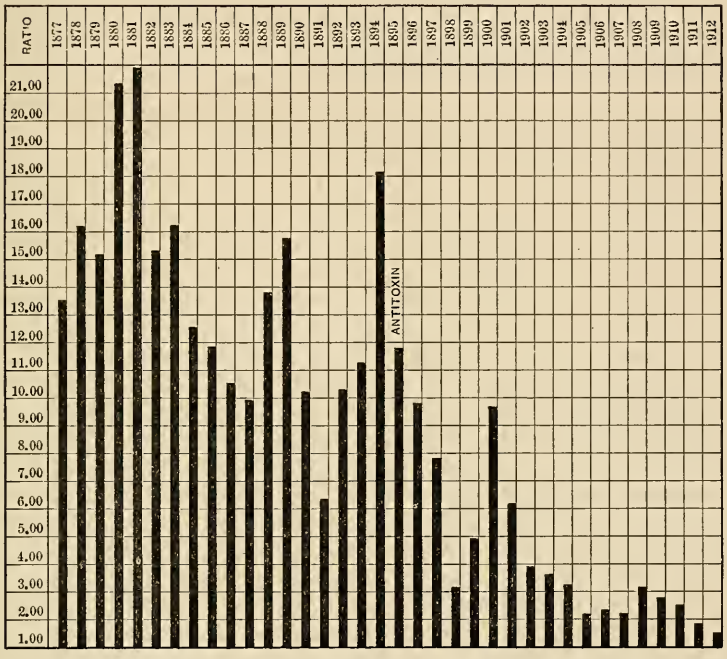


Percentage of mortality of diphtheria at the Boston City Hospital, proper, and at the South Department from 1888 to 1912 inclusive. Percentage of mortality of intubations for the same time. 1888 to 1894 no antitoxin. 1895 to 1912 antitoxin.

Unfortunately the physician as a rule is not called until there is a certain amount of membrane in the throat, and much valuable time is lost. In the report of the State Board of Health of Massachusetts for 1902 is an interesting table giving the fatality percentage of diphtheria according to the day of the administration of antitoxin. In 1433 cases in which antitoxin was given on the first day the mortality was 7.9 per cent.; when the serum was given on the second day in 3284 cases, the percentage was 6.2; when it was given on the third day in 2654 cases, the percentage was 9; on the fourth day in 1687 cases, the percentage was 12.9; on the fifth day in 864 cases, the rate was 15.9 per cent.; on the sixth day and later in 1242 cases, the percentage was 17.6. It must be taken for granted, when it was stated that antitoxin was given on the first day of the disease, that the chances are, in many instances, the physician did not see the patient until the second day, when the

symptoms were pronounced; but even with this source of error, the importance of the early administration of the serum is demonstrated. At the South Department there have been 460 cases of diphtheria among the doctors, nurses, and employees since September 1, 1895, and *there has not been a death*, which is due unquestionably to the fact that antitoxin was administered in large doses at the outset of the attacks, in many instances before there was any membrane apparent.

FIG. 16



The reduction of deaths from diphtheria is shown by chart which gives the mortality per 10,000 of the population in Boston.

MacCombie, in the Annual Report of the Metropolitan Asylums Board, London, for 1893, gives some interesting figures illustrating the advantages of the early administration of antitoxin. He says that from 1897 to 1903, inclusive, of 187 cases treated on the first day of the disease the percentage of mortality was 0. Of 1186 cases treated on the second day of the disease the mortality for 1897 was 5.4 per cent.; for 1898, 5; for 1899, 3.8; for 1900, 3.6; for 1901, 4.1; for 1902, 4.6; for 1903, 4.2 Of 1233 cases treated on the third day for the corresponding years the percentages were 11.5, 14.3, 12.2, 6.7, 11.9, 10.5, 17.6. Of 963 cases treated on the fourth day for the same years the percentages were 19, 18.1, 20, 14.9, 12.4, 19.8, 16.7. Of 1260 cases treated on the fifth day and after, the percentages are 21, 22.5, 20.4, 21.2, 16.6, 19.4, 17.3. It is an interesting fact that the mortality, when treatment was delayed to the fifth day and afterward is four times, and in some cases

five times, as great as when antitoxin was given on the second day of the disease. The statement has been made that antitoxin is not effectual after the fourth or fifth day of the disease, but the foregoing figures prove that it may be of immense benefit after the fifth day and later.

Of 1047 successive cases of clinical diphtheria substantiated by culture at the South Department the mortality was as follows:

	Cases.	Mortality. Per cent.
Antitoxin on the first day	58	.0
" " second day	253	.78
" " third day	239	5.85
" " fourth day	176	9.09
" " fifth day	110	14.54
" " sixth day	54	9.26
" later or unknown	157	7.0

The greater danger of delay in cases of laryngeal involvement is shown by the following cases occurring at the same time:

	Cases.	Mortality. Per cent.
Antitoxin on the first day	9	.0
" " second day	33	6.06
" " third day	63	15.87
" " fourth day	35	11.42
" " fifth dap	31	22.58
" " sixth day	13	30.76
" later or unknown	52	13.46

Mode of Administration.—There are four avenues of administration; (1) oral, (2) subcutaneous, (3) intramuscular, and (4) intravenous.

Oral administration is too slow and the effects too uncertain for practical use. Unless digestion is interfered with most, if not all, of the antitoxin is destroyed.

Subcutaneous injection is the method in common use. The site of injection is of slight importance but the areolar tissue beneath the angle of the scapula is perhaps the best. Here the tissue is lax, allowing distension without pain, asepsis is easily carried out, and if abscess occurs no serious harm follows. It is also satisfactory because patients cannot see the operation. There is no more discomfort than in other locations and usually less. The syringe should be thoroughly sterilized by boiling and the site of the injection cleaned with the same care as for a surgical operation. A fold of the skin is taken up between the thumb and forefinger of the left hand, and the needle plunged quickly into the subcutaneous cellular tissue. When this is done there is comparatively little pain. If the needle is put too deep there is greater pain and subsequent tenderness from the distension of the tissues beneath the fascia and a tendency to leak back because of pressure. The serum should be injected slowly and the tumor caused by it should be allowed to subside without rubbing. There are very many different syringes devised for this purpose. The simpler the syringe the better. The one used at the South Department is of glass with a glass piston and asbestos packing. The needle is attached by means of rubber tubing. This is important, because the pliability of the tubing allows a certain amount of motion if a patient struggles, and therefore diminishes the liability of breaking the needle or the syringe. The piston should be removed

from the barrel and the serum poured into it, because it is difficult to draw fluid through the needle. The piston should then be inserted, the syringe elevated, and all air driven out. The puncture should be sealed with absorbent cotton and collodion.

Intramuscular injection is advised by some because of greater rapidity of absorption, but its practical value is doubtful and its use is attended by greater pain unless very small doses are used.

Intravenous injections have been advocated in order to secure more immediate action of the toxin. Smaller doses are also required but there are somewhat greater difficulties in technique. Such treatment should not be used without some skill and experience in intravenous therapy. Tochau[1] found no benefit from this method and the clinical results are not much better. Subcutaneous injections answer perfectly well when treatment is given early, but in late cases it may be an advantage to use the intravenous route.

Dosage.—This cannot be fixed by definite rules because there is no known method of estimating the quantity of toxin. Experience and the clinical study of a large number of cases are the only grounds on which sound conclusions can be reached. In the early days of antitoxin the doses were too small, for, as an unknown quantity was being used, the fear of doing harm was always present. As time went on and as there were no injurious effects due to the use of the serum, the dose has been gradually increased. The same rule holds good with antitoxin as with any other drug, namely, that the remedy should be given until the full therapeutic action is apparent. The duration of the attack of diphtheria has a very important bearing on the quantity to be administered. The principle of antitoxin treatment is simply that sufficient must be given to secure the complete binding and neutralization of all the toxin in the tissues and blood-stream at the earliest moment possible.

The following facts should be recalled: (1) Toxin is absorbed very rapidly from the site of the infection but is rapidly removed from the blood-stream by the tissues for which it has affinity. (2) The toxin molecule is smaller than the antitoxin molecule and is more rapidly absorbed and passes into the tissues. (3) For a certain time, probably about two days, the toxin tissue combination may be broken and toxin split off if sufficient antitoxin be brought into contact. (4) The dose of antitoxin sufficient to neutralize a certain amount of toxin *in vitro* will fail to do so if the toxin is injected into the animal before being mixed with the antitoxin. Miller[2] showed in guinea-pigs in which gradual continuous absorption of toxin was secured from collodion sacs in the peritoneum that 160 times the amount of antitoxin required to chemically neutralize the toxin *in vitro* was necessary to save the lives of the pigs. It made very little difference whether the serum was given in one dose or divided doses at various intervals. (5) The size of the patient would be of importance except that the variation in the amount of toxin is so great that the body weight can have no practical influence.

In practice the dose must be estimated in each case from experience,

[1] *Therapie d. Gegenwart*, 1910, li, 48.
[2] *Journal of Infectious Diseases*, 1911.

according to the severity of the local symptoms and their duration. The dose should be given at once which will supply sufficient antibodies to bind all the toxins within twenty-four hours. A repetition of the dose is simply an acknowledgment that the size of dose was imperfectly judged as must happen with our present knowledge. The interval between doses has no influence except that the longer it is the slower is complete neutralization secured. In the South Department practically all the serum is given in the first twenty-four hours and it is rare to find evidence of advancing diphtheria after that time. The amount varies with the severity and the stage of the disease from 2000 in the very mild to 30,000 to 40,000 in the severe and from 50,000 to 500,000 units in the extreme cases. It is unquestionable that a small dose the first day will be more valuable than a much larger one later. The only evidence of sufficient antitoxin is the local clearing of the inflammation; the swelling and redness subside rapidly, the fetor and discharge cease, the membrane blanches and loosens or dissolves. This is not evidence that all the toxin has been neutralized, for sufficient may have attached itself to the nerves or muscles to later kill the patient. Ehrlich believes that the late toxic effects, such as paralysis, are due to *toxone* which has less affinity for antitoxin and consequently may escape being bound, unless much more antibodies are given than are required to bind the *toxin*. While this is not proved in clinical work, there is evidence that many after effects of diphtheria are avoided by large doses. These are not more dangerous than small ones and may be less so. Much larger doses should be given, if the subcutaneous method is used, that is the usual practice.

In the Municipal Hospital, Philadelphia, from 1895 to 1903 the mortality of 9469 cases was as follows: Antitoxin on the first day, 10.32 per cent.; on the second day, 15.82 per cent.; and on the third day 23.56 per cent. At the Willard Parker Hospital in 1895 for nine months the mortality was: Antitoxin on the first day, 10.09 per cent.; on the second day, 25.19 per cent.; and on the third day, 34.15 per cent. When these figures of the early days of antitoxin treatment with small doses are compared with present-day results the fact is clear that insufficient dosage was then used.

The development of paralysis or heart complications is evidence that insufficient antitoxin was given or that it was not given until permanent changes had resulted. No patient ill with diphtheria in the acute stage should be considered in a hopeless condition, but antitoxin should be given in large doses until he commences to improve or succumbs to the disease. When one sees a patient with membrane covering the tonsils and uvula, a profuse sanious discharge from the nose, spots of ecchymosis on the body and extremities, cold, clammy hands and feet, a feeble pulse, and the nauseous odor of diphtheria, and finds that after the administration of 20,000 units of antitoxin in two doses the condition of the patient improves slightly, and after 10,000 units more there is marked abatement in the severity of the symptoms, that when an additional 10,000 units have been given the patient is apparently out of danger and eventually recovers, one must believe in serum therapy in the treatment

of diphtheria. When one sees a patient in whom the intubation-tube has been repeatedly clogged and the hopeless condition changes for the better after the administration of 50,000 units, one cannot but be convinced of the importance of giving large doses in the very severe and apparently hopeless cases.

Small doses of antitoxin are of little avail in the treatment of grave types of the disease, and in order to obtain the best results, the serum must be heroically administered. It is true that all of the patients to whom large doses of antitoxin have been given have not recovered, but so many of them have that one must be convinced that large doses are imperatively demanded in very severe cases.

Antitoxin has been conducive of much good in the treatment of diphtheria of the eye, the most serious acute disease with the exception of gonorrhœal ophthalmia. Serum should be administered in large doses—12,000 to 30,000 units—every six hours until the membrane commences to disappear and the congestion of the eye diminishes. The pupil should be dilated with atropine and the eye irrigated every two hours with a 2 to 4 per cent. solution of boracic acid. The following ointment can be used with much benefit:

℞—Hydr. iodid. rub.	gr. j	065
Cocainæ muriatis	gr. iv	260
Atropiæ sulphatis	gr. iv	260
Petrolati	ʒj	30

A portion of ointment the size of a small pea should be put in the eye every eight hours. Attention must be given to keeping the eye clean. If only one eye is affected the other must be protected by a watch-glass. A patch of membrane that in the throat would not be of importance, in the eye might cause blindness; therefore, the necessity of the early administration of antitoxin is obvious.

Laryngeal Diphtheria.—Beneficial effects of the serum treatment in this are as marked as in the pharyngeal form. It is generally conceded that about 90 per cent. of cases of laryngeal diphtheria previous to the days of antitoxin required operative interference. The investigations by the American Pediatric Society of the effect of the serum in laryngeal diphtheria occurring in private practice showed that only 39.21 per cent. came to operation. In hospital cases the proportion is larger, because the patients are received late in the course. It is, nevertheless, true that many cases of laryngeal diphtheria are relieved without operation by means of antitoxin, and the only reason that more are not relieved is the fact that antitoxin is not given early enough or in sufficient doses. Placing the child in a steam tent sometimes seems to be of benefit. Medicated steam occasionally gives relief. The following mixture in the proportion of one ounce to a pint of water may be used in the croup kettle:

℞—Ol. eucalypti	ʒj	30
Acidi carbolici liq.	ʒj	30
Olei terebinthinæ	ʒviij	240

Only a limited amount of steam is required. A continued steam bath has a very debilitating effect, and this is always to be avoided. The air in the tent should be simply saturated with steam—not oversaturated. The sublimation of calomel has been used, but after a careful trial it seemed to the writer that it was of no particular benefit. Valuable time is lost and the strength of the patient lessened if these measures are continued for any great length of time. The chief reliance must be placed on antitoxin and operative interference.

If the dyspnœa increases, if the substernal retraction becomes more marked, operative interference is imperatively demanded. The question naturally arises whether tracheotomy or intubation shall be done.

Tracheotomy.—If the operation of tracheotomy is done early in the course of an attack of diphtheria, the results are much more satisfactory than when it is done later. The operation, however, is not devoid of danger, particularly in very young children. The trachea in a young child is a very small tube; there are numerous bloodvessels in the operative tract; and the trachea is more deeply placed and situated beneath a thick layer of fat. These conditions render the operation hazardous. As tracheotomy is an emergency operation, strict aseptic rules can not be followed. There is danger of infection not only from without but also from within. When possible, an anesthetic should be given, but in the majority of cases the condition of the patient precludes general anesthesia. Ether causes so much coughing that in some instances a little chloroform may be given, but, if given, the administration must be conducted with the utmost care. Local anesthesia can very frequently be used with satisfactory results.

There are three operations: (1) Laryngotomy, where the incision is made through the cricothyroid membrane; (2) high tracheotomy, where the incision is above the isthmus of the thyroid gland; and (3) the low operation, where the incision is made below it. The choice must depend on the age of the patient and the amount of swelling of the neck. The patient should have the head thrown back as far as possible in order that the trachea may become prominent. Incision should be made absolutely in the median line, and all bleeding vessels should be secured. When the skin and superficial fascia are divided, a careful dissection will bring into view a faint white line which is the raphe between the sternohyoid muscles. Any veins must be ligated or pushed aside. A careful dissection through the faint white line just described will expose the trachea. Retractors should be carefully held by an assistant, and the utmost care taken to avoid dragging with more force on one side than on the other. If the isthmus of the thyroid gland is exposed, it must be carefully pushed out of the way. After the trachea is exposed, it should be opened by a careful cutting motion rather than a plunging motion. A probe-pointed bistoury is very useful for enlarging the opening in the trachea, as it is impossible with this instrument to injure the posterior wall. Bose's method of performing the high operation is described as follows: "The deep cervical fascia divides into two layers just above the superior margin of the thyroid gland, these two layers forming the main body of the thyroid capsule. The point of division

corresponds exactly with the upper margin of the cricoid cartilage, which can be easily identified by touch. The nail of the left index finger is placed against the margin of the cricoid, the pulp of the finger looking downward, whereby the thyroid gland is protected, and the fascia is opened by a short transverse incision directed against the upper edge of the cartilage. As soon as this is done, a blunt hook can be introduced through the transverse slit behind the thyroid gland, which then can be drawn down with some force, exposing the two or three upper rings of the trachea. The author never saw this method fail, and, in employing it, never was compelled to cut the cricoid cartilage for want of space to limit the incision to the trachea."

In performing the low operation, or inferior tracheotomy, the same general rules are to be observed. It must be a cardinal principle to stop all bleeding before the trachea is opened. Neglect to observe this rule has sacrificed the lives of patients. After the trachea is opened, Trousseau's dilator must be introduced into the wound, the blades opened, and the tube gently pushed into the trachea. No force must be used in inserting the tube. The incision must be long enough to admit the tube easily.

When tracheotomy is done in the later stages of diphtheria there is frequently an immense amount of swelling of the neck, rendering the operation much more difficult. Owing to the inability of the patient to get air into the lungs, not only the superficial, but the deep veins are in a very turgid condition; if they are cut, there is profuse hemorrhage which must be stopped before the trachea is opened. The directions given by some authorities, when the hemorrhage is profuse, to go boldly forward and open the trachea is not good advice, for many patients have died on the table from the blood flowing into the lungs. After the tracheotomy tube is secured in position by tape, the wound should be dressed with a thin cushion of sterile gauze but so that it can be slipped under the collar of the tube. Before the introduction of the tube, if any membrane can be seen in the trachea, it should be removed with forceps. Great care must be taken in keeping the wound as clean as possible. The inner tube should be removed every two or three hours for cleansing, according to circumstances.

Plunge tracheotomy should never be done in patients under fifteen years of age, as in young patients the possibility of entering the trachea is very slight and the danger of wounding large bloodvessels very great. In adults in cases of emergency the operation may sometimes be justifiable. In the long run, the operation of tracheotomy by dissection is preferable.

After tracheotomy the irritation of the tube may cause sloughing of the trachea and adjacent tissues. Vegetations may form about the wound, seriously interfering with respiration, requiring that the tube be worn for an indefinite period. These sequelæ, however, are extremely rare. The tube should be removed at the end of three or four days even if it is necessary to reinsert it almost immediately. There is no definite time for its removal. Each case must be judged upon its merits.

Intubation.—In 1880 O'Dwyer, influenced by the high death-rate of tracheotomy, commenced his experiments on intubation. For a long

time the operation did not meet with the approval of the profession at large, but, as time went on, due to the persistent work of O'Dwyer, of New York, and Waxham, of Chicago, intubation met with marked recognition in this country and is now the accepted operation of election in cases of laryngeal diphtheria. Much has been said regarding the causation of inhalation pneumonia after intubation, but the danger of this is more theoretical than practical.

Jacobi says that previous to 1895 out of 1024 operations of tracheotomy performed in various parts of the world, but principally in Europe, the mortality was 78.52 per cent. In the 327 tracheotomy cases at the Boston City Hospital from 1864 to 1887 the death-rate was 70.95 per cent. as given by Lovett and Munro. Stern, of Philadelphia, in collating Bourdillat's statistics, gives the mortality of tracheotomy as 73.60 per cent. Waxham collected 1072 cases of intubation performed in various parts of the United States, and gives the mortality as 73.23 per cent. At the South Department, from September 1, 1895, to December 31, 1904, the death-rate of the 1553 intubation cases was 44 per cent. as compared with 73.60 in Bourdillat's tracheotomy statistics or with 73.23 per cent. in Waxham's intubation statistics.

In analyzing the 685 deaths occurring in the 1553 intubations at the South Department, it is found that bronchopneumonia caused 318 deaths, or 46.42 per cent.; that heart complications are responsible for 102 deaths; that the number of deaths from sepsis was 97; that extension of membrane into the bronchi caused 84 deaths. The total number of deaths from the causes just given is 601. The remaining 84 deaths were due to: scarlet fever occurring as a complication 24; measles 13; nephritis 21; pulmonary tuberculosis 6; cerebral hemorrhage 1; mediastinal abscess 2; clogging of tube 4; measles and whooping cough 2; fatty degeneration of the heart 4; diphtheritic necrosis of the larynx 1; abscess of the lung 5; unilateral internal hydrocephalus 1. There were 44 secondary tracheotomies with 5 recoveries. The tracheotomies were done as a last resort because intubation did not relieve the difficult breathing. Nearly 70 per cent. of the patients on whom the secondary tracheotomies were done were in a moribund condition at the time of entrance, and this accounts for the high death-rate.

Bronchopneumonia is always a very prominent factor in causing death in operative laryngeal diphtheria, but the mortality from this cause is not so high after intubation as after tracheotomy. The reason for this is probably that after intubation the air passes through the natural channels into the lungs, whereas in tracheotomy it does not. The deaths from heart complications, extension of membrane, and sepsis would have occurred after any operative procedure and cannot be attributed, directly or indirectly, to intubation. Fatal clogging of the tube occurred only 4 times in the 1553 intubations, and, therefore, it must be considered an extremely rare accident, but the possibility of its occurrence must always be considered. Accidents of a similar nature do occur after tracheotomy. Rejection of the tube by coughing occurred 566 times in the 1553 intubations. In many of the instances it was necessary to reinsert the tube immediately. In other instances the patients would

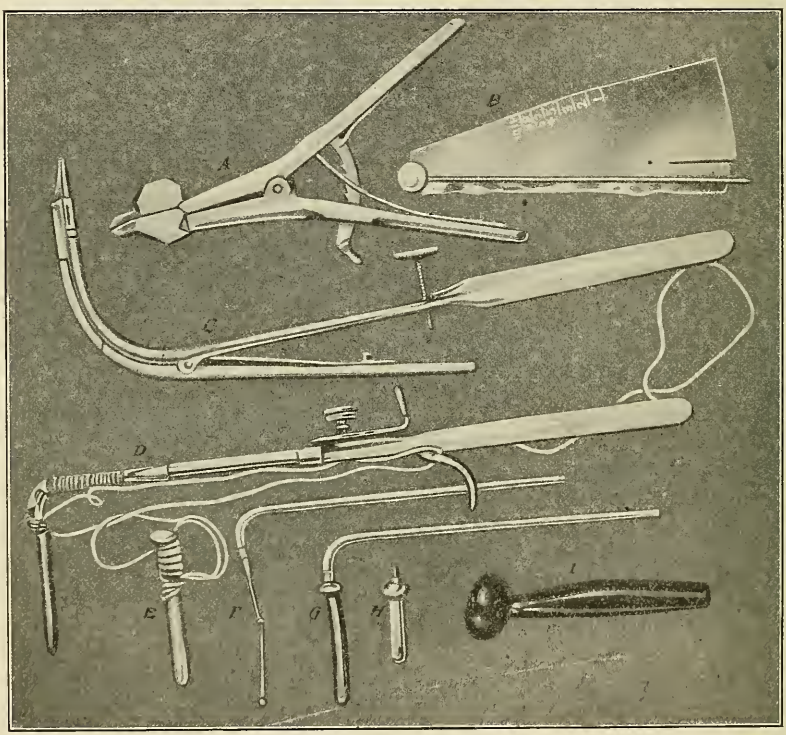
be from four to five hours without the tube, and then the dyspnœa would become so urgent that reintubation would become necessary. In still other cases, patients rejected the tube by coughing at the end of twenty-four to forty-eight hours and had no subsequent trouble, the convalescence being uneventful. This latter class is the most satisfactory of the intubation cases. There is no hard and firm rule regarding the length of time that an intubation tube should remain in the larynx. It is the writers' custom to remove the tube at the end of three or four days, depending upon the condition of the patient; frequently, however, the tube has to be immediately reinserted. The condition that causes dyspnœa sufficient to require reintubation may be spasmodic or due to collapse of the walls of the larynx weakened or paralyzed by the pressure of the tube. This latter condition must be differentiated from a stricture near the vocal cords, the result of traumatism in intubation.

Much has been said, particularly by foreign observers, of the injurious effects of intubation. Strictures, false passages, and adventitious growths have all been attributed to intubation; but if they were the result of the intubation, it was not the operation that was at fault but the operator. The liability of accidents and unfortunate sequelæ is very much less in intubation than in tracheotomy. A condition of the larynx due to stricture, the result of traumatism, requiring the permanent wearing of the tube, may sometimes occur, but a similar condition also occurs after tracheotomy. In 1553 intubations at the South Department of the Boston City Hospital there were only three instances of this nature. There were four other cases in which persistent intubation relieved the stenosis of the larynx, and the patients were discharged well. A danger in intubation that is very much overestimated is pushing down the diphtheritic membrane by the tube. If the membrane is detached by the tube, the patient will very frequently, during a fit of coughing, expel not only the intubation tube, but a cast of the larynx. If there is no relief to the breathing after intubation, the tube should be immediately withdrawn, and frequently the patient will expel a large piece of membrane. Secondary tracheotomy is sometimes required, and, therefore, when an intubation is to be done, tracheotomy instruments should be in readiness. There is no operation that is so gratifying as an intubation when it is successful. The writers have seen too many patients brought into the operating room pulseless, cyanotic, apparently dead, who, after the intubation tube was introduced and artificial respiration performed, gasped a few times, then took longer breaths, soon commenced to breathe easily and naturally, and finally recovered, not to make them earnest advocates of intubation. It is perfectly true that a patient after intubation requires more careful watching than one on whom a tracheotomy has been done, and for this reason, in sparsely settled districts, possibly tracheotomy may be better, but in hospitals intubation is the better operation.

Instruments.—The intubation set, as devised by O'Dwyer, consists of seven metal tubes or hard rubber tubes, an introducer, an extractor, a gag, and a gauge indicating the size of the tube according to age. The tubes have a large head to prevent them from slipping through the

vocal cords. In the middle of the tube is a fusiform swelling, which is supposed to assist in keeping the tube in position. Hard rubber tubes are used to a certain extent, but, except when the tube has to remain in the larynx for a very long time, are no better than the metallic ones gold plated. The advantage claimed for the rubber tubes is that salts are not deposited on their surface. The writer prefers the metallic tubes, except in adults, in whom the weight of the metal may cause annoyance. Fig. 17 shows the instruments in detail.

Fig. 17



O'Dwyer's separate instruments. *A*, gag; *B*, gauge; *C*, extractor; *D*, intubation-tube for a child two years old with the introducer ready for use; *E*, intubation tube for a child three years old; *F*, obturator showing a joint in the centre for easy removal after the tube is in position; *G*, tube for a child one year old; *H*, one of the French tubes for a child one year old, being shorter than the O'Dwyer tube; *I*, tube for an adult, made of hard rubber.

The question of feeding a patient after intubation is an important one. Œsophageal feeding may be required in certain cases. Nasal feeding should be abandoned except in rare instances, because it increases the possibility of middle-ear disease. The Casselbury method of feeding, which consists in placing the child on his back and lowering the head so that the pharynx is on a lower plane than the larynx, can frequently be adopted with advantage. Soft solids can sometimes be taken with ease. In the majority of instances sufficient food can be taken in the

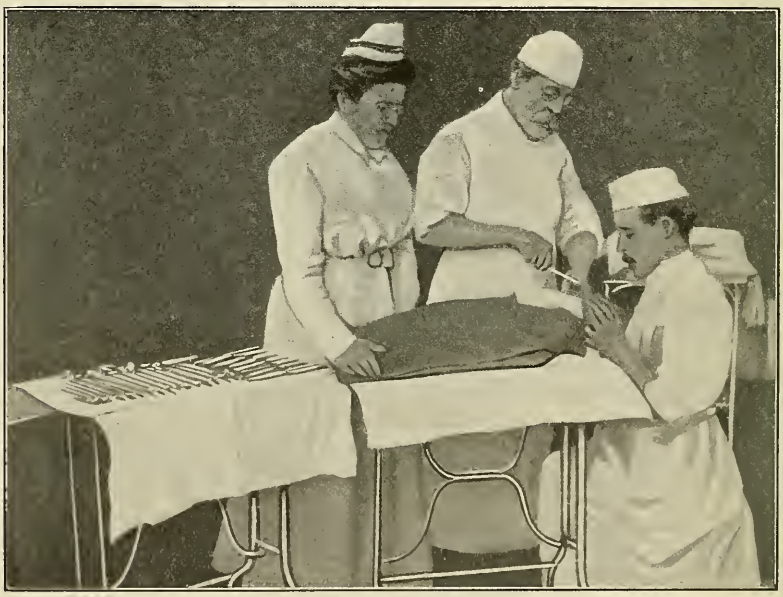
usual way if it is given slowly and in small quantities. Better results in most cases seem to follow the feeding of intubed patients just as if they had no tube, *i. e.*, drinking out of a cup in the upright position. Only liquids and semifluid food can be given.

The Operation of Intubation.—The patient's arms are placed at his side and he is wrapped in a blanket which is securely pinned. He is placed in a horizontal position with a small sand-bag under the neck. The gag is then inserted in the left side of the mouth with its jaws resting on the molar teeth, and firmly held by the left hand of an assistant who also steadies the head of the patient with his right. Great care must be exercised to prevent slipping of the gag. The operator then takes the introducer in the right hand with the index finger around the hook on the under surface of the handle, the loop of silk passing over his little finger and his thumb pressed against the button on the upper surface of the handle. The index finger of the left hand is then passed down to the epiglottis, which is hooked forward. The tube is then passed into the mouth with the handle well down on the chest of the patient. When the epiglottis is reached by the point of the tube, the handle should be given an abrupt turn upward so as to bring the tube into a horizontal position. As soon as the tube is pointed in the proper direction, the button on the upper part of the handle should be pushed forward disengaging the obturator, which must now be removed and the tube pushed into position by the index finger. The loop of silk is passed about the ear and the gag removed. If the tube is in the larynx the patient commences to cough with a peculiar sound. If the breathing is easier, the cyanosis disappears, the retraction of the thoracic walls diminishes, and the loop of silk does not shorten, it is certain that the tube is in the larynx. After becoming satisfied that the operation has been successful, the gag is inserted a second time, the index finger placed on the head of the tube, and one strand of the silk loop cut so that it can be removed. Remember that the left index finger of the operator must be a continuation of the posterior wall of the larynx; remember to make the abrupt turn; remember that no force must be used. If the tube is in the œsophagus, no cough will be heard; there will be no relief to the breathing; the silk loop will commence to shorten as the tube passes down the œsophagus. If the tube becomes clogged by membrane it must be immediately removed, and after this the patient will frequently reject a large piece of membrane. The patient may then be relieved or reintubation may be required. In case relief is not secured tracheotomy must be done and the membrane may be removed through the wound.

The first steps of an extubation are similar to those of an intubation. The extractor is passed into the lumen of the tube, the lever on the handle pressed so as to open the jaws, and the tube extracted by a reverse of the movement in introduction. Extubation is sometimes more difficult than intubation, but by gentleness and patience it can be accomplished. There are records of cases where the intubation tube has been pushed down so far into the trachea that tracheotomy was necessary to accomplish its removal. This is so rare that it cannot be used as an

argument against intubation. A patient may sometimes expel the tube from the larynx and swallow it. This is an annoying occurrence, but not one of any special gravity, as the tube is always passed by the rectum in twenty-four to seventy-two hours. Instances have occurred in which the intubation tube has been forced by coughing into the nasopharynx and removed with great difficulty, but this is extremely rare. Bayeux describes a method for removal of the tube by digital pressure or, as he terms it, by enucleation. The operator places his right thumb on the larynx of the patient just below the intubation-tube and with the left hand the head of the patient is thrown back; then with a quick motion the head of the patient is brought forward, and at the same time upward pressure is made upon the intubation-tube, which is expelled through the mouth. The writers have used it several times with satisfactory results. The great advantage of this method is that it can be used by a trained nurse in an emergency, as when the tube suddenly becomes clogged and no physician can be reached.

Fig. 18



Position during intubation.

Fig. 18 shows the postion of a patient during intubation. In certain parts of the country it is customary to intube in the upright position, but experience has taught the writers that the horizontal one is the better. Intubation of an adult is a difficult operation, but can be successfully accomplished with very satisfactory results.

If twenty-four or forty-eight hours after operative interference for laryngeal stenosis, when all the indications have been favorable, there

is a sudden rise in temperature, a profuse tenacious, mucopurulent discharge from the tracheotomy tube, or the intubation tube is clogged with a similar discharge, it is evident that membrane is extending to the bronchi, and therefore large doses of antitoxin should be administered. The failure to recognize the condition and neglect in administering large doses of antitoxin are responsible for many fatal results in operative laryngeal diphtheria. These points can not be too strongly emphasized.

It is advisable, but not essential, to place the patient on whom tracheotomy has been done in a steam-tent; it is not necessary to have a great amount of steam. Three or four layers of gauze saturated with corrosive sublimate, 1 part to 5000, over the entrance to the tracheotomy tube will moisten the air sufficiently before it enters the lungs. A patient after intubation does not requires steam except in rare instances.

Alleged Injurious Effects of Antitoxin.—A great deal has been said regarding the injurious effects of antitoxin. Many of the statements show a deplorable ignorance of the natural history of diphtheria. It is frequently said that antitoxin has a depressing effect on the heart, but failure of the action of the heart was known and recognized long before the days of antitoxin. Theoretically there is no reason to assume that antitoxin should have any injurious effect upon the heart. Practically it has been demonstrated that this organ is not affected in any way by the serum. Albuminuria has been attributed to the serum, but the evidence is against this.

The incidence of paralysis in hospital statistics has increased since antitoxin but not to the same degree that the mortality has fallen. In cases treated early with sufficient antitoxin, paralysis never occurs. Antitoxin given for immunization never produces paralysis.

Rashes occur in from 30 to 50 per cent. of the cases. The serum of some horses is more liable to produce rashes. Serum globulins, as prepared by Gibson's and Banzhaf's method, are followed by half or less the number of rashes. The amount of antitoxin in the serum has no influence. Large doses of serum are not more liable to produce reaction than moderate, but very small doses often produce no rash. Previous injection of the same kind of serum shortens the time of onset and Lucas and Gay[1] have shown increase in the tendency to local reaction.

Serum Sickness.—The by-effects of serum are chiefly:

1. *Rashes.*—(*a*) *Urticaria* occurring usually in six to eight days, at times in a few minutes. (*b*) *Erythema,* usually in from one to three weeks. It may be morbilliform, scarlatiniform, or multiform. The morbilliform may simulate measles and there may be redness of the eyes and fever. There is no coryza or invasion stage, Koplik's sign is absent, and the rash is not progressive. The scarlatiniform type often causes great difficulty in diagnosis from scarlet fever. The mucous membranes and tongue are the points in differentiation, as these are usually not involved in serum effects. (2) *Angioneurotic œdema,* chiefly of the face, hands, feet, and small of the back, usually occurs

[1] *Journal of Medical Research,* 1909, xx, 251.

about the end of the first week with urticaria; the larynx may be involved. (3) *Arthralgia,* pains on motion chiefly in the larger joints, without signs of inflammation in the first or second week. This must be differentiated from true arthritis; it causes no permanent injury. (4) *Adenopathy,* swelling and tenderness of the glands of axilla, groin, etc. The cervical glands are often involved, but it is difficult to tell whether due to serum or infection in a given case. The glands often appear and disappear suddenly. (5) *Fever,* mild or even marked, may result from serum, but not at once, and is usually associated with other signs of serum sickness, especially erythema. No fever should be ascribed to serum until all other causes can be excluded. (6) *Vomiting* and *fainting* are likely to be associated with severe urticaria. We have not seen this occur from serum unless associated with other effects. It may persist for a few days and be attended by an enlargement of the spleen. Fainting never occurs unless the patient walks about and is apparently reflex. Collapse is rare. (7) *Anaphylactic Shock.*—Sudden death has been reported, chiefly in cases of status lymphaticus and asthma, especially horse asthma. Gillette[1] collected a series of cases, and a number of others have been reported. These closely simulate anaphylaxis in guinea-pigs. In a few minutes, usually less than ten, there is intense itching of the skin and an urticarial rash. Dyspnœa quickly occurs and the patient dies from asphyxia. Fortunately these cases are rare and there has not been one in over 40,000 cases treated at the South Department of the Boston City Hospital. Death is due to spasm of the bronchioles. Full doses of atropine prevent the spasm is guinea-pigs and apparently in humans. In these cases evidence of previous sensitization as in pigs is lacking, except the association with horse asthma. Patients with asthma do not invariably die and may even be cured of the asthma. Cases have been seen by the writers of asthma and status lymphaticus as shown later by autopsy in which serum was given without any unfavorable effect. Applying the skin test as suggested by Moss or injecting very small doses of serum, as 0.1 cc., as a test and waiting fifteen to thirty minutes may detect the sensitized individuals. So rare are these unfortunate occurrences that all the harmful effects of serum since its use would not be equal to the harm which diphtheria without antitoxin would accomplish in a month in any of our large cities.

Treatment.—Complete prevention of serum sickness is impossible. Urticaria is benefited by rest, cool clothing, sedative lotions, such as 0.5 per cent. phenol in alcohol, white wash, menthol 10 per cent. in alcohol or vaseline, alkaline baths. etc., and by general sedatives as bromides. Swann[2] has recently reported the satisfactory use of adrenalin (4 to 8 minims of the 1 to 1000 solution) subcutaneously. The rash disappears in a few minutes, but often returns. The itching is often much less on its return. It disappears upon readministration. It seems to have a good effect on the other serum after-effects. The bowels should be

[1] *Therapeutic Gazette,* 1909, xxxiii, 159.
[2] *Amer. Jour. Med. Sci.,* 1913, cxlv, p. 373.

PLATE XVII

Fig. 1

A General Eruption of Erythema Multiforme.

Fig. 2

The Same Eruption after it had Commenced to Fade.

kept open and large amounts of water taken, unless there is vomiting. Persistent vomiting usually yields to complete abstention from anything by mouth and administration of salt solution by rectum.

Anaphylactic shock is probably prevented by atropine and possibly by adrenalin given at once, and is benefited by these drugs when it occurs. By giving a small non-fatal dose of serum to a susceptible person and after fifteen minutes or so giving a larger dose, the refractory stage may be attained in which any dose may be given. It does not seem necessary to apply such precautions as a routine.

Immunization.—If antitoxin is the deleterious agent that it is assumed to be by certain observers, the immunization of individuals against possible infection with diphtheria would be unjustifiable. Results have demonstrated, however, not only that the serum when given for immunization has no injurious effect, but that outbreaks of diphtheria in the children's wards of different hospitals have been prevented. In the Children's Hospital in Boston, where no infectious diseases are admitted, from May, 1897, to March, 1905, during which time 9694 patients were treated, each patient under two years of age was immunized with a dose of 750 units of serum, and each child over two years of age was given 1500 units. Previous to May, 1897, the wards and sometimes the whole hospital had to be closed on account of outbreaks of diphtheria. T. M. Rotch says that he does not hesitate to give the serum even when the patients are quite ill, and that he never has seen any bad results beyond the appearance of certain efflorescences.

In the Infants' Hospital in Boston, where children not over two years of age are treated, immunization was commenced in February, 1900. Before this, outbreaks of diphtheria were very frequent among the babies and also among the nurses and nursery maids. Since immunization was begun there has been only one case of diphtheria among the babies which was thought to have originated in the hospital. At the present time a dose of 500 units is given instead of 300 units, which was used at the outset. From February, 1900, to March, 1905, 1185 patients were treated in this institution. As a control it is interesting to know that a number of nurses and nursery maids have in the years just mentioned contracted diphtheria, but they had not been immunized, as they preferred not to be.

It is a well-known fact that patients ill with scarlet fever are particularly susceptible to diphtheria, and that frequent outbreaks of the latter disease occur in scarlet fever wards. For the past five years in the scarlet fever wards of the South Department every patient is immunized with a dose of serum of from 1000 to 2000 units, depending upon the age. The result has been that there have been no outbreaks of diphtheria in these wards, although there have been a certain number of positive cultures with no constitutional manifestations. Immunization lasts only about twenty-one days, and, therefore, it is necessary to reimmunize at the expiration of this time.

The beneficial results of antitoxin in the treatment of diphtheria would seem to have been sufficiently demonstrated to convince the intelligent practitioner of the importance of using this remedy in the

treatment of each and every case of diphtheria. The statements regarding immunization should also be convincing.

Active Immunization.—This was suggested by Theobald Smith by mixtures of toxin and antitoxin but has not been tried in humans. Such active immunization probably often occurs in antitoxin treatment of clinical diphtheria (Park). Immunization of children by means of toxin applications on cotton in the nostrils was used by Blumenau[1] with fair results. Immunization by means of vaccine was tried by Petroschky[2] in hundreds of children of whom only one developed diphtheria. Active immunization is still in the experimental stage. Its successful practical use is what is most required for the control of diphtheria.

Carriers.—No satisfactory means have been found of ridding carriers of bacilli. Tonsillectomy, adenectomy, and removal of foreign bodies and carious bone have been followed by rapid cure. Local applications designed to benefit the underlying disease of the mucous membrane are of more value than antiseptics directed against the bacilli. Antitoxin has no action on the bacilli, although chronic nasal diphtheria will often clear bacteriologically as soon as the slight toxin irritation is eliminated. Schiotz reported a cure from spraying the throat with pure cultures of *Staphylococcus aureus* and several have confirmed his results. De Witt[3] could find no batericidal action from the staphylococcus or its products and its action is supposed to be by displacement or overriding. No results have followed its use in twelve virulent and avirulent carriers in our wards.

Hewlett and Nankivell[4] have reported cures in from four to thirty-three days in 12 out of 18 carriers, mostly complicating scarlet fever. They used a solution of bacterial substance prepared by grinding the bacilli in intense cold and filtering. Of 12 carriers in our wards, 4 became negative in two weeks by the use of diphtheria vaccine, in doses of 1,000,000 to 10,000,000 every four to six days. Petruschky[5] reported the treatment of 6 cases with injections of diphtheria bacilli killed by chloroform gas. Four of the cases were treated during early convalescence and became negative in five to twenty-nine days, one of the others (bacteriological) cases became negative only after over a year of intermittent treatment.

[1] *Jahrbuch f. Kinderheilkunde*, 1911, lxxiv, No. 1.
[2] *Zeitschrift f. Städtehygiene und Gesundheitstechnik*, 1912, Nos. 1 and 2.
[3] *Journal of Infectious Diseases*, 1912, x, 24.
[4] *Lancet*, 1912, clxxxiii, 143.
[5] *Zeitschrift. f. Städtehygiene u. Gesundheitstechnik*, 1912, Nos. 1 and 2.

CHAPTER XIX

ACUTE POLIOMYELITIS

By E. FARQUHAR BUZZARD, M.D., F.R.C.P. (Lond.)

Etiology.—Distribution.—Acute poliomyelitis is a disease of wide if not universal distribution, as it is known to occur on every continent. Judging from medical literature, it would seem that North America and Scandinavia suffer far more severely than many southern countries.

Sex.—Among children the two sexes are about equally affected, but several observers, including Gowers, state that after adult age is reached, males are more frequently victims of the disease than females.

Age.—The large majority of cases occur in the first five years, after which the liability diminishes progressively up to the third and fourth decade. Its occurrence is almost unknown after forty years of age. The question of an intra-uterine attack is not settled, but the writer has seen (with Dr. F. E. Batten) an instance in which that diagnosis appeared to be justified.

Season.—Barlow and Sinkler were the first to point out the undoubted influence of season, and it is now generally agreed that in the hot summer months cases are much more common than at other times of the year. Out of 452 cases collected by Barlow, Sinkler, Gowers, and Starr, 369 had their onset in June, July, August, September, and October, and all the chief epidemics have been observed during the hot season.

Trauma.—Trauma has so long been regarded as a possible cause for many diseases of the nervous system that it attracts some attention. There is no evidence that trauma can play any important role in this disease, although parents very frequently remember some fall or blow preceding the onset. It is possible that a central hemorrhage may be produced by a severe trauma, and that the resulting symptoms may be those of an atrophic local paralysis, but they are not examples of acute poliomyelitis. Changes of temperature, prolonged bathing or paddling, may be predisposing causes, but the fact that the disease is more prevalent in hot weather should displace "chill" from its position in the lay mind as an exciting agent.

The relationship of the specific fevers of childhood to acute poliomyelitis has been the subject of attention. It is generally agreed that the disease sometimes follows, at varying intervals, measles, scarlet fever, diphtheria, and other fevers. There are, however, plenty of instances of one acute specific fever following quickly on another without any suggestion forthcoming that the later condition is a result of the earlier one. Moreover, Gowers is right when he says, "The initial general disturbance is constantly mistaken for an independent general disease, and the opinion is often maintained after the discovery of the

paralysis, which is then supposed to be of secondary origin." The victims of acute poliomyelitis are, generally speaking, healthy if not robust children, on whom the paralysis falls with particularly cruel and unexpected suddenness. There is no evidence to support the view that teething even favors the development of the disease beyond the fact that the period of the first dentition is also the period of life when acute poliomyelitis is most rife.

Bacteriology.—Landsteiner and Popper, in 1909, successfully inoculated two monkeys with the spinal cord from fatal cases of poliomyelitis. Flexner and Lewis (Rockefeller Institute, New York) infected monkeys and produced a disease similar to that in the human. They were able to transmit the disease through a series of monkeys by way of the brain, peritoneal cavity, and circulation. The virus passes through the finest filters, resists glycerinization and considerable degrees of cold. It has been recovered from the nasal and pharyngeal mucosa of infected patients and animals and also from persons not suffering from the disease who have been in contact with sufferers. There is evidence to show that it may pass through the intestinal canal with no impairment of its vitality, that it may be carried by insects, and that it can be found in the dust of rooms in which infected monkeys have lived.

Attempts to produce the disease in animals other than monkeys have been largely unsuccessful, but the virus may be recovered from the tissues of inoculated rabbits which have not developed the characteristic symptoms and lesions themselves. The serum of human beings and monkeys who have survived an attack contains neutralizing principles which confer immunity to second attacks, and this serum has been shown to neutralize emulsions containing the active virus when mixed with them. On the other hand the injection of an immune serum into animals affords little or no protection to subsequent infection.

These remarkable discoveries throw much light upon the possible methods of contagion not only by direct contact but by healthy carriers, domestic animals, and insects. On the other hand an active method of fighting the established disease has not yet been elaborated.

Still more recently Flexner and Noguchi by special methods have cultivated the organism of the disease. "The minute colonies are composed of globular or globoid bodies, averaging in young cultures 0.15 to 0.3 of a micron in size. The bodies appear in a variety of arrangements: single, double, short chains, and masses. In older cultures certain bizarre forms have been noted. Monkeys have been inoculated with the twentieth generation of the culture; typical experimental poliomyelitis resulted."

Pathology.—The morbid changes in the early days of the disease will be dealt with first. In this connection certain broad statements may be made: (1) The morbid anatomy of epidemic cases is similar to that of sporadic cases. (2) The changes in the adult are the same as those in the child. (3) In all cases the extent of the disease as shown by examination of the tissues is greater than could be inferred from the clinical symptoms. If a patient dies from the effects of paralysis of the limbs and trunk muscles, it is safe to prophesy that anatomical evidence

of the disease will be found also in the brain stem, and perhaps even in the cerebral and cerebellar hemispheres.

To the naked eye the meninges covering the central nervous system are hyperemic. The substance of the cord and brain, and particularly the gray matter, appears vascular, and the latter may, in the more severe cases, be hemorrhagic and softened. In section of the spinal cord the gray matter stands out unusually well on account of the numerous cells it contains, and all vessels, in both white and gray matter, are rendered prominent by their engorgement and by the dark staining of their perivascular sheaths.

The *histological anatomy* may be discussed under the following heads: (1) Meninges, (2) White Matter, (3) Gray Matter, (4) Central Canal.

1. *Meninges.*—It is usual to find the vessels of the soft meninges full of blood, and in the more severe instances the membranes contain an excess of cells, chiefly lymphocytes, in the tissue meshes between the vessels. In many cases this cellular infiltration is only evident in the lumbosacral region, but in a few it extends to the higher parts of the cord and even to the basal meninges. It never gives rise to an appearance of pus to the naked eye, nor do the cells themselves resemble leukocytes. The amount of cellular infiltration is usually greater on the anterolateral than on the posterior surface of the cord. In the cases examined by the writer the majority of the cells in the pia arachnoid were of the mononuclear type; a smaller number showed the various intermediate stages between the lymphocytic and the plasma-cell characters, and only a small percentage of other cells, among which were a few polymorphonuclear leukocytes, were observed. That this meningeal infiltration is not a feature of fatal cases only is proved by the fact that a lymphocytosis of the cerebrospinal fluid has been demonstrated in non-fatal cases. It is probably an indication of considerable severity in the morbid process.

2. *White Matter.*—The columns of nerve fibers do not suffer much, although some scattered degeneration takes place, chiefly in the anterolateral columns in the neighborhood of the gray matter. The neuroglial cells undergo some change. The most striking feature is the intense cellular infiltration of the walls of the vessels, which radiate from the surface inward. The cells lie really in the lymphatic space existing between the media and adventitia and in the meshes of the latter coat. Only very occasionally are foci of inflammatory cells seen in the white matter away from the bloodvessels, and these are of small size.

3. *Gray Matter.*—The vessels resemble those of the white matter in that their outer walls are packed with cells chiefly of the mononuclear type, and this applies in the spinal cord, not only to those derived from the anterior spinal arterial system, but also to those from the posterior root vessels, and applies equally to arteries, veins, and capillaries. In virulent cases small hemorrhages from the capillaries are found; in other cases, which have survived some days or weeks, evidence of blood stasis and thrombosis is forthcoming in the form of tissue necrosis and softening. In addition, the gray matter is the seat, particularly in the

anterior horns of the cord, of extensive cellular infiltration of varying density.

The nerve cells of the anterior horns, of Clarke's column, and of the posterior horns all suffer, in varying degree. Owing to the greater vascularity of the anterior horns, the cells of that region are generally most affected, but marked changes are frequently found in the other parts. Speaking generally, those ganglion cells undergo the greatest change which are most closely embedded in the masses of inflammatory cells, but this rule has its exceptions, and occasionally healthy looking nerve cells are met with in areas of intense inflammation. It is very unusual to encounter definite degeneration of ganglion cells which are far removed from the foci of disease. The myelinated fibers of the gray matter, as well as the cell processes, are partially or completely lost in the inflammatory areas.

4. *The Central Canal.*—In many cases it is impossible to detect changes in the contents or walls of the central canal, but the inflammatory areas of the gray matter may extend to the ependymal cells.

The spinal roots and the posterior root ganglia may be the site of cellular infiltration similar to that in the meninges and cord. The ganglionic cells undergo chromolytic and destructive changes in some instances.

The examination of those who have died months or years after the attack shows that the results of inflammation are similar to those in other tissues. In some parts resolution may have taken place with the loss of a few or no ganglion cells; in other parts fibrosis has led to deformities of the gray matter and to complete loss of its cellular elements; in other cases the necrosis may have produced actual cavities in the cord. The Weigert-Pal method of staining may reveal some evidence of scattered sclerosis in the white columns, particularly in the neighborhood of the gray matter.

Nerves.—The efferent fibers of the anterior roots and of the spinal and cranial nerves of which the ganglion cells have been destroyed undergo the usual secondary degeneration, but there is no evidence to show that the morbid process ever involves directly the peripheral nerves.

Muscles.—The changes in muscles paralyzed by an attack resemble in almost every respect those consecutive to an experimental neurectomy. They constitute a simple atrophy. The connective tissue seems to be proportionately increased with the shrinkage of the muscle fibers. At a later date examination may reveal changes which are not seen after simple nerve section, but which are not always present or only in varying degrees in individual muscles. Lipomatosis is the most striking, the fat in some cases replacing whole bundles of fibers, and even whole muscles. The presence of hypertrophic poorly striated fibers is not uncommon, and these may perhaps denote incomplete degeneration of central nerve cells. In other instances a whole muscle may be represented only by a fibrous band.

Pathogenesis.—An acute inflammation affecting the most vascular parts of the spinal cord, with the clinical evidence of an acute febrile disorder occurring sporadically and in epidemics, and resembling the

acute specific fevers, justifies the view that acute poliomyelitis is an infective disorder. Recent experimental work has confirmed this view and has determined its specific characters. It is clear, however, from the behavior of the ganglion cells that these are not specifically susceptible to the influence of the virus, but suffer rather from the effects of inflammatory changes in surrounding tissues. If the poison has any selective action, this is probably vented upon the neuroglia, seeing that the gray matter is particularly rich in this tissue and that the peripheral nerves, devoid of neuroglia, remain directly unaffected.

The writer feels that acute poliomyelitis has at least as strong claims as some of the acute specific fevers to be regarded as one of them, and welcomes its inclusion in their ranks. It has the constitutional disturbances, the age incidence, the seasonal exacerbations, the sporadic and epidemic types, the immunity from second attacks, associated with the obscurity of bacterial origin, which are shared by measles, scarlatina, and varicella; on the other hand, it presents the inflammatory lesion of a particular tissue which is met with in typhoid fever, diphtheria, and variola. It resembles the latter particularly in its permanent cicatrices and their deforming results.

The relation of acute poliomyelitis to certain forms of acute encephalitis has attracted considerable notice since Strümpell and later Marie drew attention to the probable identity of the pathological process in the two diseases. That their morbid anatomy is strikingly similar has been shown, but still more interesting are the recorded occurrences of the two diseases in the same individual or in two or more members of the same family at the same time. In many of the larger epidemics, cases of encephalitis have been found among the cases of poliomyelitis, and paralysis of the cranial nerves has occurred either with or without spinal symptoms in the same individuals. There is abundant evidence to show that encephalitis may be, and often is, excited by the causal agent of poliomyelitis, although it is not yet clear what determines the incidence of the disease upon the brain or spinal cord.

Symptoms.—Initial Stage.—In the autumn a child previously healthy is noticed to be out of sorts, is restless, refuses food, and is found to have a temperature of 100° to 103°. He may vomit or may have one or more convulsions. In the course of one or two days it is noticed that he has lost power in both legs and can no longer stand or run about. The arms are also paralyzed during the next few hours. With the onset of the paralysis the child resents handling, crying when any attempt is made to move him, and, even when at rest, appearing in some distress. Another day or two and all constitutional disturbance has passed off, the arms are already beginning to recover power, and the movements of one leg are certainly less completely lost than those of the other. Evidence of pain is only elicited on passive movement of the lower limbs. At the end of ten days or a fortnight there is much less pain even on handling; the arms have recovered power, although they are flabbier than formerly, the better leg has regained movements at the hip and knee, dorsiflexion of the ankle being still absent, but the other leg hangs limp and lifeless. Examination reveals the presence of some wasting

and greater flaccidity in the paralyzed muscles, and the helpless leg is colder than its fellow. A stronger faradic current than usual is required to produce any contraction in the affected parts, and the reaction to galvanism is less brisk than in the arms. The patellar and Achilles-jerks are absent on the one side and can only just be elicited on the other. Cutaneous sensibility is perfect everywhere. Retention of urine, which was present for the first day or two, has now passed off, but the patient, if in the first or second year of life, does not learn to hold his urine for some time. Lumbar puncture finds the spinal fluid at high tension and possibly containing an excess of lymphocytes.

This is the common history of the first two weeks in an attack of medium severity. Prodromal symptoms may last from a few hours to a week, and vary in different epidemics. Sometimes catarrh of the respiratory tract is more conspicuous than symptoms referable to the gastro-intestinal system, such as diarrhœa and vomiting. Fever is nearly constant, but may remit before evidence of paralysis sets in. Sweating, drowsiness and irritability, or general hyperesthesia have been prominent features in many cases. In milder cases the constitutional disturbance may be absent or so slight as to escape notice, and if often forgotten in after days, the mother declaring that the child was perfectly well all through. Only one lower limb may be paralyzed at the outset, and in the course of a few days the disability may be limited to one or two muscles below the knee. In more virulent forms all four limbs and the trunk muscles are rapidly and completely paralyzed, with the result that the child is dependent on its diaphragm and accessory muscles for respiration. If this condition does not hastily mend, bronchopneumonia or bronchitis is more than likely to bring about an early fatal termination.

A still more fulminant type somtimes occurs—and probably occurs at times without the true diagnosis being made—in which the paralysis quickly spreads upward, and, by involvement of all respiratory muscles and perhaps those of deglutition, ends the patient's life in the course of thirty-six to forty-eight hours. Head retraction is not uncommon in such cases, and leads to the suspicion of meningitis. The age has no material influence on the clinical picture of this stage, with the exception that convulsions are less common in older subjects. On the other hand, an adult is better able to describe the sensory side, and on questioning will complain of pain, often dull or gnawing in character, in the back, and of sharp neuralgic pains, increased by movement and often of several days' or even many weeks' duration, in the affected limbs. However variable the different cases may be in the rapidity of onset, in the progress of the paralysis, and in associated disorders, the disease is characterized by the fact that the initial paralysis is invariably in excess of what remains at the end of a few days or weeks.

In regard to the reflexes it is the rule that all muscles which show any degree of paralysis lose their tendon-jerks at first. If atrophy does not supervene, the jerks return, but if wasting and reaction of degeneration follow the paralysis, the jerks are lost for many months if not permanently. The superficial reflexes of the trunk are preserved in

most cases unless the abdominal muscles are paralyzed. The plantar reflex is lost when the muscles moving the toes are paralyzed, but if these are intact, stimulation of the sole will produce generally a flexor, but in some instances an extensor response. When the latter occurs it signifies some extension of the disease into the pyramidal tracts. An extensor response may be associated with an increased patellar-jerk, or even with ankle-clonus in rare cases, the extensors of the knee and the flexors and extensors of the ankle having escaped paresis.

Attempts, which are mainly unsatisfactory, have been made to classify various types of the disease, and spinal, cerebral, bulbar, meningitic, and neuritic forms have been described. In the opinion of the writer, it is unwise to lay much emphasis on predominating symptoms in particular cases, as such a procedure tends to cause confusion between the clinical and anatomical aspects of the disease. We do not talk about crural, brachial, or facial types of measles or smallpox. It must be remembered that a more or less diffuse inflammation of the central nervous system with its membranes is the basis of the malady, and that particular symptoms are merely indications that in one part or another the reaction has reached such a degree as to interfere seriously with local function. In a case which is put under the "spinal" category, the inflammation is not necessarily, and probably not frequently, limited to the spinal cord, and the same criticism may be applied to so-called "cerebral" types. This is demonstrated by the postmortem examination of recent cases, and it may be reasonably inferred that diffuse, transient, and slight disturbances of function easily overlooked, occur widely in most cases in which attention is rivetted on those parts most seriously and permanently affected.

On the other hand, for purpose of diagnosis, it is desirable that symptoms of meningitis, for instance, should not induce an observer to exclude the diagnosis of poliomyelitis, or that pains and tenderness in the muscles of the extremities should not lead to a hasty conclusion that peripheral neuritis is the cause of paralysis. An ascending form of poliomyelitis has frequently been diagnosed and recorded as Landry's paralysis, with the result that the literature of both diseases is full of confusing errors.

It is important, however, to remember that abortive types undoubtedly occur, and that these may be recognized when the disease is prevalent. Such cases, with fever, vomiting, drowsiness, and catarrh, but with very transient or no paresis, should be suspected as possible sources of infection.

Stage of Repair.—This cannot be said to have very well-defined limits, its length varying, but it begins roughly at the end of the second or third week and lasts until the end of a year or eighteen months after the onset. During this time the full extent of the permanent damage is ascertained, some muscles gradually shrink and become useless, others after a period of paralysis and atrophy slowly become restored to a condition approaching, if not equal to, their former competence, and the effect of the disease on the growth and nutrition of the limbs becomes more and more apparent.

Examination now reveals unmistakable wasting of the affected muscles resulting in almost complete loss of soft tissue in certain regions, or in other cases, chiefly young children, in the replacement of the muscles by fatty deposits. The skin over these parts is generally colder, more purple in hue, and either more dry or more clammily moist than elsewhere. Lax muscles lead to alterations in joints, and with the occurrence of permanent shortening in other muscles, combine to produce serious deformities. The chief factor in the production of the shortening is the natural unopposed action or tone of a healthy muscle, its antagonist being paralyzed. This may be assisted by an increase in the connective tissue of the muscle due to the degeneration of some of its fibers when it has not completely escaped. Bones to which many paralyzed muscles are attached cease to grow in children, although in rare cases actual elongation of a bone, due, probably, to traction on the epiphyses, may take place. As a general rule, shortening is present and trophic changes in the bone may be demonstrated.

The electrical reactions during this stage are of importance, especially with regard to prognosis. Those muscles which, although paralyzed, never completely lose their faradic excitability may be confidently expected to recover their function. Muscles which lose their faradic excitability, and in which the galvanic response is slow and more easily produced by the anodic than the kathodic closure current, have undergone the reaction of degeneration. Their fate hangs in the balance until either (1) the galvanic response becomes quicker and more natural, which is of good omen and precedes the return of voluntary contraction and faradic excitability, or (2) the galvanic response becomes gradually more difficult to obtain and finally disappears, denoting a complete and permanent destruction. Some reference may be made to the incidence of permanent paralysis. The statistics of Duchenne and Seeligmüller show that in about 55 per cent. of cases one leg, in about 17 per cent., one arm or both legs in about 5 per cent. all four limbs, and in 2 per cent. both arms, are affected. The trunk muscles, innervated as they are by the less vascular dorsal segments of the cord, are not so frequently paralyzed. On the other hand, the muscles of respiration are commonly involved in the most virulent and fatal cases.

Taking the limbs separately, it is noticeable that the dorsiflexors of the ankle, the extensors of the knee, and the extensors of the hip are more often affected than their respective antagonists, and that the muscles moving the shoulder and elbow are more prone to disablement than the intrinsic muscles of the forearm and hand. Generally speaking, there is no tendency to symmetry in the results of the disease on the limbs of the two sides; on the contrary, asymmetry may almost be considered a characteristic feature.

Permanent Results.—After eighteen months have passed nature may be considered to have brought about any repair of which she is capable, and the remaining effects must be regarded as permanent, unless artificial means of modifying them can be employed. The clinical picture is now one of deformities, the most common of which are talipes equinovarus and valgus, pes calcaneus, contracture of the knee in the flexed position,

scoliosis, and lordosis. The growth of healthy parts emphasizes the small size and shortening of the paralyzed member or members.

Diagnosis.—Any difficulty is only rarely a serious one in the acute stage and in young infants. A febrile disturbance associated with a painful condition of the limbs, especially evoked by handling, and with a pseudoparalysis, is produced by rickets, scurvy rickets, syphilitic epiphysitis, osteomyelitis, and rheumatic fever, and must be differentiated from acute poliomyelitis by general examination, by inspection of the affected parts, by attention to the reflexes, and, if necessary, which is not often, by electrical stimulation of the muscles. In very acute cases poliomyelitis may simulate meningitis, owing to the rigidity of the back and neck muscles, the vomiting, and the convulsions, but the simulation is only a temporary one, and the early appearance of flaccid palsy with the disappearance of the other symptoms puts an end to the difficulty. Probably some acute cases of this kind die in the first few hours, and then the diagnosis can only be made postmortem, although the examination of the spinal fluid may afford a clue.

From *multiple peripheral neuritis* the diagnosis is chiefly based on the gradual onset, the symmetrical incidence of the paralysis, and the presence of more or less sensory disturbance in this disease. A cerebral monoplegia, especially of the leg, may simulate an old lumbar poliomyelitis at first sight, owing to the shortening and diminutive size of the limb with some circulatory disturbance and perhaps a tendency to talipes equinovarus. However, in spite of the general wasting, the limb preserves its natural contours, the reflexes are those associated with spastic conditions, and the muscles respond to mechanical and electrical stimulation. Reference has been made to certain acute spinal atrophies, which come on very suddenly, without constitutional disturbance, limited from the first to a single region. These are probably examples of a vascular thrombosis or hemorrhage, and, except for the history of onset, can not always be differentiated from acute poliomyelitis when once established. A rare disease, amyotonia congenita, may be mistaken for the results of poliomyelitis, but close observation will show that true paralysis is not present, although the tendon reflexes are not obtained and the muscles may be unresponsive to faradism.

Finally, the comparative rarity of poliomyelitis in the adult and the occasional ascending character of its symptoms has not infrequently led observers to make a diagnosis of Landry's paralysis. Unfortunately this has not always been corrected when the examination of the tissues has revealed gross inflammatory changes in the spinal cord.

Prognosis.—In the acute stage the prognosis as regards life depends upon the extent of the disease, with particular relation to the respiratory musculature. If the patient survives the first few days without grave respiratory difficulty, the prognosis may be regarded as favorable in the absence of complications such as bronchopneumonia or intestinal troubles. In the second stage the probable recovery of power must be estimated from the electrical reactions.

Treatment.—We are unacquainted with any method of combating the acute attack, and must be content to treat the initial stage similarly

to that of any other acute infective disease. When the disease is epidemic and constitutional disturbances suggest the possibility of an attack, the administration of hexamethylenamine is worth a trial. Confinement to bed, a diaphoretic, and a purge are indicated, and pain may be relieved by the exhibition of salicylates, phenacetin, or, in severe cases, when rest is interfered with, of an opiate. While the fever lasts the diet should be light and easily digestible. Attention should be paid to the bladder and a catheter used if there is any evidence of retention. Great care must be employed to avoid any risk of bronchial or pulmonary complications. In the event of the respiratory musclature becoming embarrassed, inhalations of oxygen are indicated, and artificial respiration may be carried out.

After the first two or three weeks there are several important points:

1. Passive movements of paralyzed parts should be performed two or three times daily, and changes of position should be enforced, for the purpose of preventing contractures.

2. The patient should be encouraged to attempt movements of paretic parts every day. The adult will do this according to instruction, but ingenuity must be exercised to induce an infant to make the effort. The attachment of a bell or rattle to the paralyzed limb is sometimes effectual.

3. All paralyzed limbs should be warmly clad with woollen garments and massage should be practised daily. In cold weather hot bottles may be employed to keep up the temperature of the lower extremities.

4. Electrical treatment may be employed, although it is not as important as the measures already detailed. The object is to make the paralyzed muscles contract and to retain their power of contraction until their innervation is restored. The galvanic current must be employed, the kathodic being used as the mobile electrode. In young children it is well to begin with an inappreciable current, which can be gradually increased in strength from day to day until a definite contraction is elicited. When all the benefit possible has been obtained from these measures, and it is justifiable to expect continued even if very slight improvement up to at least eighteen months after the onset, the question of artificial aid in the form of instruments, tenotomies, or other surgical procedures must be raised. Instrumental aid is often effectual in allowing a child to walk by fixing one or more joints, but care should be taken that the apparatus is as light as possible, and that any shortening in the limb is compensated by additional thickness in the sole of the boot. The employment of light celluloid splints within three months of the onset of paralysis often enables children to walk and use their limbs before heavier instruments are justifiable. Frequent alterations are necessary with the growth of the child. Tenotomies are useful for the purpose of putting a limb or part of a limb into an advantageous position.

The grafting of portions of a healthy muscle into the tendon of a paralyzed muscle has been advocated, but the writer has seen no case in which the object aimed at had been really attained. Nerve-grafting deserves a more conscientious trial, and may give good results in suitable cases. In certain instances the patient will be better served by an amputation stump than by a badly deformed foot.

CHAPTER XX

GONOCOCCUS INFECTIONS

By RUFUS COLE, M.D.

Introduction.—The role which the gonococcus plays in human infections is now known to be an important one. The consideration of the local infections caused by gonococci in the genital tract does not belong here; but apart from these infections, gonococci not infrequently induce lesions in other parts of the body, either primarily, by extension, or by metastases. The following pages deal mainly with these extragenital lesions, the great variety and gravity of which are astonishing. By the laity, gonorrhœa has been largely considered as a mild, and aside from the social aspects, unimportant disease. But the physician, who regards its far-reaching consequences, which are hardly secondary to those of syphilis, does not consider it so lightly.

Gonococcus.—This organism was first described by Neisser (1879), who saw it in the purulent secretion from cases of urethritis and conjunctivitis neonatorum. Its specificity remained somewhat in doubt, however, until its growth in pure culture by Bumm, in 1885.

The gonococcus, as it usually appears in pus, occurs in pairs, each individual having a form usually described as like a biscuit or coffee bean, the flat sides of the individuals being approximated. Such a pair usually measure in the long axis 0.8 to 1.6μ and in cross diameter 0.6 to 0.8μ. As seen typically in gonorrhœal exudate, many of the pairs are found within leukocytes. In contradistinction to streptococci and staphylococci, these organisms decolorize when stained by the Gram method. Lastly, they do not, under ordinary conditions, grow on the usual culture media, but require a medium containing uncoagulated albumin. The above points are the main differential ones. It must be insisted upon that morphology alone is not sufficient to distinguish this organism. Streptococci, especially when obtained from animal exudates, may occur in biscuit-shaped pairs. Most closely related, however, to gonococci are *Micrococcus meningitidis* and *Micrococcus catarrhalis*. In morphology and staining properties, both of these resemble the gonococcus, but differ from the latter in growing on the ordinary culture media. While these organisms are not likely to cause errors in the study of urethral exudates, in the more unusual extragenital lesions this possibility must always be borne in mind. On the other hand, gonococci in cultures do not always show the typical form mentioned above, but may appear in somewhat oval pairs, or as rounded individuals.

These organisms grow best on a culture medium composed of hydrocele fluid, one part, and nutrient agar-agar, two parts, or even better on

a medium composed of human blood, one part, and agar-agar, three parts. Up to the present time no animal except man has been shown to be truly susceptible to infection with the gonococcus.

The work of Torrey has demonstrated conclusively that various races of gonococci show different biological characteristics, as determined by their agglutination and precipitation reactions, and by the fixation of complement test. By these reactions the various races may be divided roughly into groups. This demonstration is of great importance in its bearing on specific therapy.

The production of a toxin has been demonstrated by de Christmas, Wassermann, and others. There is still a difference of opinion as to the exact nature of this toxin, whether it is an endotoxin and so only set free by the disintegration of the bacteria, or whether it is a toxin produced in media by the metabolism of the organisms. The part which this toxin plays in the production of infection is still undetermined.

Diagnosis of Gonococcus Infections by Means of Specific Immune Reactions.—The demonstration of the etiological agent in the lesion is the best and only absolutely certain diagnostic procedure. In many cases this is impossible, and considerable success has been obtained by demonstrating the presence of specific antibodies in the blood of the patient, or by producing a specific reaction in the patient by the injection of killed organisms. The direct demonstration of antibodies, such as agglutinins, bacteriolysins, opsonins, etc., has not proved especially valuable, but better results have been obtained by using fixation of complement as a means of demonstrating the presence of antibodies. This was first used in the diagnosis of gonococcus infections by Cole and Meakins, and has been very thoroughly studied and employed in a large series of cases by Schwartz and O'Neill.[1] Their reports should be consulted as to the best technique. A polyvalent antigen should be employed, and when this is done, it has been demonstrated that a positive reaction is obtained in a large proportion of cases, not, however, before the fourth week following the onset of the infection. This positive reaction usually does not entirely disappear until seven or eight weeks after cure. A negative reaction does not necessarily indicate that the infection is not gonococcal in origin, though it offers considerable evidence in favor of this. The reaction is most valuable in the diagnosis of late and chronic complications.

A second specific diagnostic procedure consists in the production of a reaction in the body by the injection of killed cultures of gonococci. These reactions are of several kinds: (1) A general reaction may occur, consisting in an exacerbation of the general symptoms with headache, fever, and sometimes vomiting. While this reaction may occur with very large doses even in normal persons, with moderate-sized doses, such as 500,000,000 gonococci, Irons and others have shown that the occurrence of such a reaction affords evidence that the patient is suffering from a gonococcal infection. Fromme has considered this reaction of diagnostic value in gonococcal infections in women, though other

[1] *Amer. Jour. Med. Sci.*, 1911, cxli, p. 693, and 1912, cxliv, p. 369, 815.

observers disagree with this position. (2) In addition to the general reaction, there frequently occurs, following the injection, an exacerbation of the symptoms and signs in the local lesion. In arthritis, for instance, there is an increase in the local pain and tenderness, with an increase of the œdema and redness of the skin. In urethritis there may occur an increase of the exudate, and the exudate, if previously free from gonococci, may again show their presence. (3) In the infected patient, about the site of injection of the killed culture, there frequently follows marked redness, tenderness, and œdema, while in the uninfected patient these are usually entirely lacking. (4) Lastly, it has lately been shown by Irons that following the application of a drop of the glycerin extract of gonococci, to which extract he has given the name "gonococcin," to the slightly abraded skin, there occurs in the infected patient, after a few hours, the appearance of a papule surrounded by a zone of hyperemia. Usually in twenty-four hours the reaction has reached its maximum. Normal persons show a very slight focal reaction as contrasted with the marked reaction seen in persons with gonococcal infections.

Clinical experience with any one of these methods is as yet insufficient to permit of a conclusive discussion as to their value in diagnosis. It may be stated, however, that a positive reaction obtained in any of the ways mentioned offers evidence of the existence of a focus of gonococcal infection within the body; the absence of a reaction is not conclusive evidence that such a focus does not exist.

Specific Treatment of Gonococcus Infections.—In the treatment of secondary lesions due to gonococci, two methods of specific treatment have been attempted: (1) The use of specific antisera derived from immunized animals, and (2) treatment by the injection of killed gonococci—vaccines.

Serum Treatment.—Owing to the biological differences in different races of gonococci, immune sera, to be efficacious, must be polyvalent. Several such sera have been tried, but the reports as to their value are conflicting. In the acute stages of certain complications, good results are said to have been obtained.

Vaccine Treatment.—A considerable number of attempts have been made to treat gonococcus infections by the repeated subcutaneous injection of killed cultures of gonococci, hoping to produce an active immunity and in this way to destroy the organisms. So far the treatment of primary gonococcus infections in the acute stages by this means has yielded disappointing results. The results have been somewhat more promising in the treatment of the more chronic and secondary lesions. Much more may be expected from this method of treatment if the vaccines are prepared from the same race of organism causing the infection or, at least, if polyvalent vaccines are used. No definite rules can be given at present for the best dosage or best time intervals between treatments. Control of these factors by determination of the opsonic index is unsatisfactory.

Primary Lesions.—The usual seat of infection by the gonococcus is one of the mucous membranes. Most frequently this is in the genital tract, the urethra in the male, the urethra or more rarely the vaginal

or uterine mucosa in the female. Why there should be this susceptibility of these tracts is entirely unknown. The infection of these membranes may be acute or it may have a very chronic course, lasting for months or even years, with occasional exacerbations. Often the infection does not remain localized, but passes by direct extension into the structures immediately surrounding the original seat. Prostatitis and epididymitis occur with great frequency in the male. The work of Wertheim and others has shown the great frequency with which inflammation of the tubes, ovaries, and pelvic peritoneum occurs in women. While these lesions are treated especially by the genito-urinary and gynecological specialist, and are considered in books devoted to diseases of the genito-urinary tract, it must be remembered that these infections may be productive of the most obscure general manifestations. Young men are not infrequently treated for typhoid fever who are suffering from prostatitis, and women with pelvic peritonitis are treated for malaria and other infections.

A most unusual train of symptoms may be associated with a chronic prostatitis. Aside from the neurasthenic features and indefinite pains, which so often are but a manifestation of this condition, the patients may complain of abdominal pain, even of such severity as to suggest a renal calculus. Or the pain may be in the legs, like that of sciatica, or in the lumbar region, or the main symptom may be a severe pruritus ani. The obscure symptoms associated with salpingitis and pelvic peritonitis in the female are better known. Other localities in which primary infections by the gonococcus have been demonstrated are the eye, the rectum, the mouth, the nose, and possibly in external wounds of the skin. As compared with the genital tract all of these localities must be quite resistant to infection with this organism.

Gonorrhœal Conjunctivitis.—The absolute proof that this might be due to the same etiological agent as urethritis was given by the discovery by Neisser of gonococci in the purulent secretion from such inflamed eyes, and their cultivation by Bumm and Wertheim, and finally the experimental production of ophthalmia with pure cultures. The demonstration that the conjunctivitis of the newborn is due to this organism through infection from the mother during birth is of very great importance. Next to urethritis, conjunctivitis is the most frequent primary gonococcal lesion, and formerly its results were only slightly, if at all, inferior to importance in the genitourinary lesions. The introduction by Crédé of the prophylactic use of silver nitrate in the eyes of the newborn forms one of the most important accomplishments of scientific medicine. Before this time, in the obstetrical institute in Leipzig, 10.8 per cent. of all newborn children suffered from conjunctivitis. Since then the frequency has diminished to 0.1 or 0.2 per cent. The great importance of this disease is shown by the estimation that 10 per cent. of the cases of blindness in Europe are due directly to it.

Conjunctivitis in the Adult.—The healthy conjunctiva of the adult must possess a relative degree of immunity to infection with this organism, since, notwithstanding the very widespread distribution of urethritis

and the frequent opportunities for the infectious material to be carried to the eye, cases of conjunctivitis in the adult are relatively rare. The opportunities for prolonged and severe infection of the eyes during childbirth are much greater than are at all likely to occur in adult life, and the natural protective mechanism of the eye in the adult is more highly developed than in the infant.

The condition usually starts with great suddenness and intensity. Following the early signs of conjunctivitis, great swelling of the lids develops, the conjunctiva becomes roughened, and the secretion becomes purulent and frequently forms a grayish membrane upon the eyeball. Usually but one eye is affected at first, and the first care of the physician should be directed to protecting the other one. This should be covered by a shield, the inner edge of which should be sealed with collodion, and every effort should be made to prevent the infective secretions gaining entrance to the healthy eye.

Treatment.—Cold compresses should be applied to the affected eye and very frequent irrigations with mild antiseptic solutions, such as boracic acid or potassium permanganate (1 to 5000). After the great swelling has disappeared and the membrane is no longer present, 2 per cent. silver nitrate may be applied several times a day. It is of the greatest importance that physicians should not treat lightly any case of conjunctival infection where there can be any possibility of its being gonococcal in origin. The great danger is the involvement of the cornea and the formation of ulcers leading to scar formation with resulting total blindness.

Conjunctivitis Neonatorum.—The onset is usually within three days after birth. The symptoms do not differ essentially from those occurring in the adult, except that in general the course is milder. The bulbar conjunctiva is usually not so seriously involved, and involvement of the cornea, while still frequent in improperly treated cases, is apparently less common than in adults.

Treatment.—The treatment is essentially that to be employed in adults. It is important to institute prophylactic measures in all newborn infants, both in private practice and in hospitals, whether the occurrence of gonorrhœa is suspected or not. The child should be bathed, without allowing the bath water to touch the eyes, and then into each eye a drop of 1 per cent. silver nitrate should be instilled.

Gonorrhœal Proctitis.—This condition is said to occur in 25 to 30 per cent. of all cases of gonorrhœa in women. It is a frequent complication of vulvovaginitis in children. The mode of infection is usually, first, from the vaginal secretion, which is permitted to flow over the perineum into the rectum; second, from the use of soiled nozzles, rectal tubes, or specula; third, by the rupture of an abscess into the rectum; or lastly, a result of abnormal coitus. The first is undoubtedly the most common and explains the greater frequency of this form in females.

There are two groups of cases of gonorrhœal proctitis: first, the acute, with severe pain in the region of the anus and with tenesmus, frequently associated with the formation of ulcers in the rectum; and second, a group of cases in which the symptoms are very mild, and to

which the attention of the physician is frequently not drawn unless the condition be suspected and looked for. Cases of either the first or second group may run a prolonged course and lead to the formation of stricture. König has stated that gonorrhœa causes rectal stricture with greater frequency than syphilis. Perirectal abscess, secondary to proctitis, occasionally occurs.

Treatment.—In the acute stages the condition should be treated by irrigations of silver nitrate (1 to 4000) or potassium permanganate (1 to 5000). The sphincter should be dilated, and if ulcers are present these should be touched with the silver nitrate stick.

Gonorrhœal Stomatitis.—While gonorrhœal infection of the rectum is usually recognized by its direct association with infection of the genitalia, the nature of such an infection of the mouth may be difficult to determine. It is not sufficient for the demonstration of gonococci from this situation, that only morphology and staining reactions be considered, owing to the frequent occurrence in the mouth of *Micrococcus catarrhalis* and other organisms closely resembling gonococci. The mode of infection may be by the transference of infectious material on the fingers from the urethra or conjunctiva, or the mouth may be primarily infected by improper practices. In infants, in whom this infection is most common, it may occur from the mother during birth.

Symptoms.—The lesions usually consist of round, slightly elevated, gray-white spots scattered over the tongue and cheeks. They vary in size from that of a pinhead to that of a pea, or these smaller spots may be confluent over larger areas. There is no ulceration. The tongue is swollen, red, and dry. Often the mucous membrane about the teeth is also swollen. The breath is foul. In some cases infection of the sublingual glands has occurred.

Diagnosis.—This depends upon the history, the rapid course, the absence of ulceration, but above all on the cultivation of the organism directly from the lesions.

Treatment.—This consists in antiseptic washes, careful cleansing of the mucous membranes of the gums and about the teeth, and in severe cases the application of silver nitrate.

Local Wound Infections.—Gonococcus infection of incised wounds may occur, as following arthrotomy for gonococcus arthritis. Such infection of the umbilical cord in infants has been described. Isolated instances of similar local infections have been described, but are undoubtedly rare.

General Infection.—It is now generally recognized that the local lesions at the portals of entry and in the adjacent structures are not the only ills attributable to the gonococcus. Evidence is rapidly accumulating to show that from these local lesions gonococci not very infrequently invade the blood. This is shown by the cases in which gonococci have been cultivated from the circulating blood as well as by the strong probable evidence shown in the cultivation of gonococci in foci far distant from the primary seat of infection. Why in certain cases gonococci invade the blood and cause a septicemia, or are carried to distant parts, setting up secondary infections, is not known. It was formerly thought

that infection of the posterior urethra was always the preliminary event in a general infection. But it is now known that a general infection may be secondary to a conjunctivitis or other local primary infection.

Gonococcus Septicemia.—The first probable demonstration of the invasion of the blood by gonococci was made by Wertheim, who, in sections made from an infected bladder, demonstrated the gonococci invading the small venules. The absolute proof rested with the cultivation of these organisms from the circulating blood by Thayer and Blumer in 1895. Since this time a considerable number of cases have been reported in which a gonococcus septicemia has been conclusively demonstrated. A study of 29 septicemia cases collected by the writer shows that they may be divided into four groups:

1. The cases in which endocarditis has been present: It is somewhat surprising to find that only 11 of the 29 cases belong to this group. In most of them the clinical features were those of malignant endocarditis, with fever, sweating, chills, and frequently the association of septic infarcts. In 1 of them, however, there was only a mitral insufficiency of moderate grade, and this patient recovered. All but one of the remaining patients died.

2. The cases in which local suppurative lesions in the internal organs or in the subcutaneous tissue have occurred and the general features have been those of pyemia: In this group belong 6 of the cases. Among the local lesions were subcutaneous abscesses, abscess of the prostate, suppurating inguinal buboes, suppurative seminal vesiculitis, epididymitis, parotitis, peritonitis, pleurisy, and pneumonia. Of these, 3 died and 3 recovered, 2 of the latter after surgical intervention. In one occurring in the Johns Hopkins Hospital, the blood cultures were made 5 days after the operation for peritonitis. Probably in this case the general infection occurred secondarily, as a terminal event.

3. Cases with no metastatic local infections, or only very mild and relatively insignificant ones: There were 10 of these; all recovered. In one patient, seen by the writer, three months after an acute attack of gonorrhœa, there was continuous fever, lasting seven weeks, with headache, general malaise, an enlarged spleen, and general features resembling typhoid fever. The Widal reaction was negative and blood cultures showed the presence of gonococci. The patient made a perfect recovery and the absence of endocarditis is evidenced by the fact that there were no signs of any cardiac lesion five months later. This case shows that gonococci may cause a septicemia of moderate grade, the general features of which are not unlike those of typhoid fever.

4. Cases of gonorrhœal puerperal septicemia: The exact role which gonococci play in puerperal fever is still unsettled. Some authors state that as many as 25 per cent. of all cases of puerperal fever are due to gonococci. This includes, however, the cases in which the infection is only a local one. Absolute proof that these cases are gonococcal in origin is in most instances lacking. Of the 29 cases of septicemia collected by the writer, only 2 were of this form.

Of the entire 29 cases, 12 died, 16 recovered, and the result in 1 was not stated. The prognosis, therefore, is not necessarily hopeless when

gonococci are cultivated from the blood. The prognosis is worse when endocarditis is present.

Method of Making Blood Cultures.—In making cultures it is advisable that at least 10 cc. of blood be obtained, under proper precautions, from one of the larger veins, in a sterile syringe, and this be added to melted agar in the proportion of 1 to 2 or 3, and that the mixture be then immediately poured into Petri dishes and allowed to solidify. After from twenty-four to forty-eight hours the small colonies may be easily recognized. Owing to the susceptibility of the gonococcus to moderate heating, it is important that the temperature of the melted agar to which the blood is added be not above 40° C.

In suspected cases, in which the presence of the bacteria in the blood can not be demonstrated, the other specific methods of diagnosis mentioned above may be tried. It is doubtful whether in the present state of our knowledge it is justifiable to make a positive diagnosis of gonococcus septicemia in the absence of positive blood cultures.

Treatment.—The treatment of gonococcus septicemia does not differ from that of septicemia due to other pyogenic agents. If local suppurative foci of infection be present, these should be treated surgically if they are accessible. Specific treatment by vaccines or antigonococcus serum may be tried in such cases.

Secondary (Metastatic) Lesions.—Besides the cases showing secondary lesions in distant parts of the body in which the metastatic nature of the infection is rendered probable by the demonstration of gonococci in the circulating blood, there are other cases in which such definite proof is wanting, but yet in which the gonorrhœal nature of the local focus is shown by the cultivation of gonococci from it, or is rendered probable by the clinical association of the secondary focus with the primary lesion. There are several views as to the origin of these foci: first, that the infection is through the blood; second, that it is through the lymphatics; and lastly, that the lesions are due to toxins. It seems probable, however, that these extragenital lesions are usually due to the transmission of a very few bacteria through the blood and their localization in *loci minoris resistentiæ.*

A word should be said in regard to the treatment of all metastatic foci. While carrying out appropriate local treatment, the primary focus should not be overlooked. This is most often a chronic prostatitis or vesiculitis in the male, or salpingitis in the female. It has been claimed by some that treatment of such primary foci may stir up the infection, cause increased reinoculation, and so do more harm than good. There is little evidence for this, and the writer has never seen any harm come from proper treatment of the primary focus. Of course, violent measures should be avoided as far as possible.

Heart and Vessels.—Endocarditis.—The association of endocarditis with urethritis, and especially with gonorrhœal arthritis, was recognized as early as 1847 by Ricord. The proof that the same etiological agent was concerned in the production of the endocarditis as in that of the urethritis was furnished only by the isolation of gonococci in pure culture from the circulating blood during life, and their demon-

stration in smears from the thrombus on the heart valve after death, by Thayer and Blumer[1] in 1895. Since then a large number of cases have been reported in which the absolute bacteriological proof of the specific nature of the endocarditis has been furnished.

Pathology.—Little is known of the exact pathological changes in the cases of simple endocarditis which usually recover. In the more severe cases in which the evidence as to the specific nature is more convincing, and in which there have been frequent opportunities for postmortem study, the conditions are better known. These have shown the usual appearance of ulcerative endocarditis with polypoid thrombus formations. In many cases the extent of the latter has been enormous, with great fungoid masses extending from the surface of the valve, and by some this has been regarded as somewhat characteristic of this form of endocarditis. It may occur, however, in other forms, and is not infrequently seen in malignant streptococcus endocarditis. As to the valves involved, it is of interest that in a number of the cases in which the pure gonococcal nature was probable, the right heart was involved. In 15 cases collected by Thayer the following valves were affected:

Left heart	aortic	7	Right side	tricuspid	1
	mitral	2		pulmonary	2
	both	2			
		11 = 73.3 per cent.			3 = 20 per cent.

Both sides, all four valves: 1 = 6.6 per cent.

Of 49 cases collected by Kulbs, 36 were in men and 12 in women. Involvement of the right side of the heart occurred in 10 cases, 20 per cent. The valves involved were:

Aortic in	28	Aortic and mitral in	3
Mitral in	8	Mitral and tricuspid in	1
Pulmonic in	6	Aortic, tricuspid, and mitral in	1
Tricuspid in	1	All valves in	1

The above statistics show the apparently greater frequency of involvement of the right heart in gonococcal than in simple endocarditis, even greater than that in other forms of ulcerative endocarditis, in which it is well known that in general there is a greater tendency to right-sided involvement than in simple endocarditis.

Clinical Features.—Young adults are most liable to the disease, though cases have been reported in children and in the aged.

There are two groups of cases showing clinical features corresponding to the anatomical lesions: (1) In one group the symptoms are those seen in other forms of simple endocarditis. It is difficult to be certain that these are truly gonococcal in nature, though the report by Prochaska of a case of simple mitral insufficiency with recovery, in which the organisms were obtained from the circulating blood during life, renders it quite probable that the cases reported as simple gonococcal endocarditis have been really such. It is quite possible that certain of the

[1] *Arch. de méd. expér. et d'anat. pathol.*, 1895, vol. vii, p. 701.

cases of chronic endocarditis in which no definite history of an acute infection can be obtained, originated from a mild urethritis. (2) The symptoms in the cases of malignant endocarditis which have been carefully studied are essentially the same as those occurring in cases due to other pyogenic organisms. The fever is usually intermittent or remittent; chills and sweating occur frequently. There is usually a moderate leukocytosis and a rapidly progressive anemia, at times as marked as that associated with general streptococcus infections. Arthritis is frequently associated with the endocarditis, though this is not invariable, and in many cases septic embolic infarcts may develop, or there may be involvement of the serous membranes, pericarditis, pleurisy or peritonitis. These two groups, however, are probably not sharply limited, and cases probably occur of all degrees of severity from the mildest to the most severe.

Diagnosis.—This is made in the same way as in other forms of endocarditis. Its gonococcal nature may be rendered probable by the associated lesion at the portal of entry, but the definite proof can only be obtained by the cultivation of the organism from the blood or by the other specific methods of diagnosis.

Treatment.—This does not differ from that of other forms of endocarditis. The considerable frequency with which this condition occurs should cause one to consider as suspicious all patients with urethritis having a continuous or irregular fever. In these the heart should be carefully and frequently examined, and, if there is any suspicion of cardiac involvement, the patient should be put to bed, an ice-bag placed over the heart, and the diet restricted. As in other forms of endocarditis, rest of the heart is probably the greatest factor in preventing advance of the process. As to the time which patients should be kept in bed after the acute stage one may stay as long as possible.

Pericarditis.—This occurs much less frequently than endocarditis, but may be present with endocarditis. The amount of exudate may be very slight, or, as in a case described by Councilman, very large, the pericardium containing at autopsy 800 cc. of a hemorrhagic exudate.

Myocarditis.—Changes in the myocardium of greater or less extent have been mentioned in association with most of the cases of endocarditis. Some have shown necrosis and embolic abscesses. Councilman has reported a case with severe hemorrhagic necrosis in the muscle wall, in smears from which gonococci could be demonstrated. Another case of suppurative myocarditis has been reported by Iwanoff.

Phlebitis.—French writers especially have drawn attention to the occurrence of phlebitis in association with gonorrhœa. The pathogenesis of the condition is not certain. There have been no observations as yet to show whether the condition is due to the direct action of gonococci upon the wall of the vein, that is, whether it may be considered a specific gonococcus lesion, or only an associated phenomenon. Considering the great prevalence of gonorrhœa, one must be careful in attributing all lesions which occur during the course of a urethritis to the gonococcus. The occurrence of phlebitis without any apparent cause and unassociated with gonorrhœal affections must be kept in

mind. However, the direct association with urethritis and the frequent association with other well-known complications of gonorrhœa, such as arthritis, in many of the reported cases make it extremely probable that the gonococcus alone may induce a true phlebitis. Heller has collected 26 cases of gonococcal phlebitis, in 15 of which arthritis was also present.

The veins of the lower extremities are most likely to be involved, especially the internal saphenous. The clinical features do not differ from those of other forms of infectious phlebitis. Fever may or may not be present. Œdema follows the venous obstruction. In 16 out of 26 cases complete recovery resulted. In 1 case gangrene resulted and amputation was necessary.

Treatment.—This is the same as in other forms of phlebitis, wrapping the extremity in cotton, immobilization, and elevation.

Arthritis.—This is probably the most frequent and also the most important complication of gonorrhœa.

Etiology.—At present two views are held as to the direct cause of the arthritis: first, that it is due to the action of soluble toxins elaborated at the seat of local infection; and second, that it is due to the localization in the joints of gonococci which have gained access to the general circulation, or have passed from the local lesions to the joints through the lymphatic channels. The main evidence in favor of the former view is that adduced by Wassermann, who after injecting the toxin into his own body, noticed pain in his limbs and joints, which lasted a couple of days. That a true inflammatory reaction occurred in the joints is not stated. While possibly the action of toxins may explain some of the cases, the evidence in favor of this view is not very convincing.

On the other hand, the view that the lesion is due to the localization of gonococci in the joints is now well established by the cultivation of these organisms from the joints in a large number of cases. It must be admitted, however, that from many of the infected joints no gonococci can be grown, even though the cultures are made with the greatest care. It is probable, however, that the organisms are often present in the tissues, even where the examination shows the exudate to be sterile.

By what channels the gonococci reach the joints from the local lesions is in most cases not demonstrable. In a few cases of arthritis the organisms have been cultivated from the circulating blood, but these have been the more severe cases, usually associated with other features of septicemia. It is altogether probable, however, that the path is through the blood current. The exact conditions under which the organisms leave the local lesion and are carried to distant parts are not known. There is much difference of opinion as to why the joints are seats of predilection for the secondary localization of these bacteria. The frequency with which slight injuries occur in the joints, so rendering them *loci minoris resistentiæ*, may be one factor, but it cannot be the only one. It must be remembered that in other forms of general infection, joint lesions occur not infrequently.

Pathology.—König has made the following classification of the forms of gonorrhœal joint involvement:

I. Hydrops gonorrhoicus.
II. Arthritis sero-fibrinosa et catarrhalis.
III. Arthritis purulenta (empyema of joints).
IV. Arthritis phlegmonosa (essentially the peri- or para-articular form).

These forms, however, pass gradually one into the other and there is no sharply dividing line. The moderately severe cases which are most frequently seen at operation are not simple hydrops and yet have not reached the stage of empyema. In joints of moderate severity there is quite marked œdema and infiltration of the peri-articular tissues. On opening the joint a large amount of turbid fluid escapes, which not infrequently contains large masses of fibrin. The synovial membrane is much injected and the villi are markedly swollen and red. Usually no erosion of the cartilage or bony change is present. In the more severe forms the exudate is very purulent and marked erosion of the cartilage, and even of the bone may occur. In the later stages, where there is marked limitation of movement, there is usually an extreme grade of thickening of the capsule and peri-articular tissues, but occasionally there is true bony ankylosis with marked thickening of the bones. The occurrence of osteophytes is rare, but they are undoubtedly present in some cases.

The *x*-ray examination in the acute stages usually shows only peri-articular swelling, but no changes in the bones or cartilages. In the more severe cases cartilaginous and bony erosions may be seen and later thickening and ankylosis. Kienböck has pointed out that marked atrophy of the spongy portion of the bones occurs. This, however, does not indicate any inflammatory process in the bones themselves, and is not peculiar to gonorrhœal arthritis.

Frequency.—Various writers estimate that from 2 to 5 per cent. of all patients with gonorrhœa suffer from this complication. It must be borne in mind, however, that many patients leave the genito-urinary clinic at the onset of arthritis and are treated in medical wards, that many infections are very mild and the patient or physician does not associate the joint trouble with the urethritis, and finally that many cases are wrongly diagnosed by the physician, so that probably the frequency is greater than that given above. By some writers it has been considered the most frequent form of arthritis.

Arthritis may follow any form of local infection with gonococci. As urethritis is by far the most frequent local gonococcal infection, arthritis is most frequently associated with this, but cases of arthritis complicating ophthalmia in infants or vaginitis in young girls are not rare. Arthritis following the inoculation of "tripper pus" into the eyes of trachoma patients for the cure of this condition has been described.

Age.—As urethritis is most common during early adult life, gonorrhœal arthritis occurs most commonly during this period. No age, however, is exempt. It occurs in infants, secondary to ophthalmia neonatorum.

Sex.—This complication occurs more frequently among men than women. Possibly the greater frequency of genital gonorrhœa among

men than women largely explains the difference, but it is probable that many cases in women are unrecognized. This is especially true of postpuerperal arthritis, many cases of which are gonococcal in origin.

Clinical Course.—There are three forms of gonorrhœal arthritis: that seen by the genito-urinary specialist, that seen by the physician, and that seen by the surgeon. Every genito-urinary surgeon is familiar with patients who, during an attack of acute urethritis, complain of a little tenderness or pain in one or more joints. Little or nothing is to be discovered on examination of the joints, there is very little fever, and in a few days the pains disappear. In a second group, or rather a second stage during which the physician is usually consulted, the joint pains are more severe, the joints are red, hot, and swollen, there is fever, and the patient is often forced to go to bed. These are the cases which are so often mistakenly called acute articular rheumatism. There is a third stage, in which the brunt of the attacks falls on one or two joints, or the earlier stages may be so slight and transient that the patient does not mention them in giving the history, and the whole picture is that of an acute suppurative arthritis. These are the patients who consult the surgeon, and it is for this reason that the picture of this malady is painted in such dark colors by many surgeons.

Onset.—The view is sometimes expressed that arthritis is more likely to occur during the course of a chronic gleet than during an acute urethritis. This view does not receive support from our statistics, as in all but 9 of our 43 male cases, the arthritis followed the onset of acute urethritis in from one day to four months. In 23 of the cases, the arthritis occurred during a first attack of urethritis. The onset of the arthritis may follow the urethritis very quickly. In 1 patient the urethral discharge was noticed three days following exposure to venereal infection, and on the following day he had pains in the knees and ankles. A case has been described by Resnikow in which a girl, aged sixteen years, developed urethritis and arthritis four days after marriage to a man suffering from gonorrhœa.

On the other hand, the arthritis may occur during a second, or even later attack of urethritis. Eleven of our patients gave a history of from one to four previous attacks of urethritis, and in 6 of these arthritis had occurred with the previous attacks of gonorrhœa. The view has been expressed that if arthritis occurs during an acute urethritis, subsequent attacks are most likely to be accompanied by arthritis. There are not enough available statistics to decide this point. In many patients, on the other hand, no history of local infection can be obtained. This is especially true in women. In men there is usually a history of a past attack of urethritis; sometimes an unrecognized chronic gleet is present. Nine of our cases were not associated with acute urethritis, but in all but 4 there was a history of attacks one to ten years previously; and in all but 1 there were evidences of a chronic urethritis in the shape of "tripper-faden" in the urine or the presence of a urethral discharge containing gonococci.

The first symptom complained of is usually pain in the smaller joints of the hands and feet, though occasionally one of the larger joints, as the

knee, may be involved from the beginning. The pain is frequently first noticed when the patient arises in the morning. Occasionally a history of exposure to cold and wet previous to the onset is obtained. This occurred in 7 out of our 50 cases. In this series a history of trauma was rare. Slight general malaise may occur for a few days before the onset, but the pain may begin with very great suddenness and without warning. In one instance the patient was perfectly comfortable, eating his dinner, when he was seized with a very severe pain in his hip, which so increased in intensity within a very few minutes that he was in agony and required morphia to relieve the very acute suffering. A chill may occasionally occur at onset, and profuse sweating is not very uncommon.

General Features.—*Joint Involvement.*—Contrary to the usual statement, in almost all cases more than one joint is involved. In all but 3 of our 50 cases there was *polyarthritis*. On the other hand, the records in the surgical service of the Johns Hopkins Hospital show a considerable proportion of cases with monarticular involvement. Among 252 cases collected by Northrup, 56 were monarticular; of 348 cases collected by Julien, 143 were monarticular. The probable reason for this discrepancy is that many are seen only in the later stages, when the disease is frequently localized in one or two of the larger joints, and the early history is not carefully considered. In many cases the early involvement of the small joints is slight, with few or no objective features. In other cases, however, a number of the joints show considerable swelling, redness, and tenderness. The polyarticular involvement may last only for a few days, or a number of the joints may remain swollen during the entire course. Contrary to what occurs in rheumatic fever, it is seldom that after recovery occurs in a joint it again becomes inflamed. All the joints are not necessarily involved at once, however. One joint may recover and others be involved in succession.

A study of the relative frequency of involvement of the various joints shows that it is about the same in gonococcal arthritis as in rheumatic fever, except in the case of the temporomaxillary joint, which is not infrequently involved in gonorrhœal arthritis, and with extreme rarity, if at all, in rheumatic fever.

The affected joints are usually held quite firmly fixed. The pain and tenderness may be severe and constant, but are usually markedly increased by motion. The pain may be partly due to the stretching of the capsule by the effusion, as in many cases aspiration markedly diminishes the pain. It may be severe, however, where the effusion is very slight. The effusion is usually most marked in the larger joints, especially the knee, in which case there is riding of the patella. But no matter how large the effusion, one practically never sees the marked relaxation of the ligaments, with resulting dislocation and deformity, that sometimes occurs in the severe suppurative joints. The swelling is not always confined to the joint, but in the elbow may extend upward to the shoulder and downward almost to the wrist. Often on palpation points of special tenderness are found. These are more often over the insertion of the tendons than directly over the bony prominences, as is seen in tuberculous arthritis. Frequently crepitus is obtained on

passive motion, though this is not constant. Often the crepitus is due to involvement of the tendon sheaths.

Fluid aspirated from the affected joints may be quite clear or it may be distinctly purulent. Cytological examination of the fluid shows a preponderance of polymorphonuclear leukocytes. The fluid frequently has a slightly greenish tinge, a feature first pointed out by König. This is not characteristic of this form of arthritis, however; it may be present in rheumatic fever. The writer has seen brownish, probably blood-stained fluid aspirated from a joint which had not previously been aspirated. Generally the more severe the joint involvement, the more purulent is the exudate, though this is not an absolute rule.

Fever.—There is usually an irregular fever of moderate grade. In 50 cases the highest temperature was 103.5° F., but usually the temperature did not rise over 102° F., in some not over 100° F. It is important to note that the fever may entirely disappear, while the local condition in the joint remains unchanged.

Blood Changes.—There is usually some anemia, but not so marked as in rheumatic fever. A moderate grade of leukocytosis is the rule. There is no apparent relationship between the degree of leukocytosis and the severity of the lesions.

Diagnosis.—In certain cases this is difficult. The conditions with which it is likely to be confounded are rheumatic fever, other forms of septic joints, tuberculosis, gout, and the acute stages of arthritis deformans. The presence of urethritis, especially with the demonstration of gonococci in the discharge, is of great importance, although the possibility that the urethritis may be associated with some other form of arthritis must always be kept in mind. Entire failure to obtain relief of the pain by the use of salicylates is of assistance in differentiating from rheumatic fever.

In the early stages the course does not aid materially. Certain of the smaller joints are not infrequently involved. The persistent involvement of one joint, however, especially if there be much effusion, is in favor of the condition being gonorrhœal. Involvement of the temporomaxillary joint occurs more frequently in gonorrhœal arthritis. Sweating is often not so pronounced in gonorrhœal arthritis as in rheumatic fever, while cardiac involvement is more frequent in the latter. Examination of the blood gives little assistance. In doubtful cases, especially in the later stages, the *x*-ray examination is often of aid, especially in the differentiation from tuberculosis. In gonococcus infections of the joints the outline of the bones usually remains distinct, even though the cartilages are eroded, while in tuberculosis the outline is often entirely gone and the bones appear as if fused. In gonococcus and other acute infections the atrophy of the bone is quite uniform, but in tuberculosis it is focal and irregular, and on the plate the bone appears mottled and "pitted."

The demonstration of gonococci in the affected joint forms the only absolutely positive means of arriving at a diagnosis.

Treatment.—In the mild attacks the main treatment should be directed to the genital lesion. Whether in these cases reinfection from the genital

lesion is constantly occurring is not known, but there is little doubt that the patients recover more quickly when there is active and successful treatment of the primary lesion. Some think arthritis only occurs in association with a chronic focus, usually in the prostate, Cowper's gland, and seminal vesicles. Massage of the vesicles is recommended and some advise draining the vesicles. Certainly in the presence of a local focus, this should always be treated. The joints should also be protected from injury, and this is best accomplished by putting the patient to bed. Wrapping the infected joints in cotton, or the application of compresses soaked in a lead and opium solution, often relieves the pain. In the acute stages the joints should be kept perfectly at rest, and this can best be done by fixation on splints. It is very doubtful whether drugs do any good. Many physicians employ potassium iodide, with what are thought to be beneficial results. In a doubtful case it is well to try salicylates, but if it be gonorrhœal arthritis, little result can be expected.

The use of immune serum in this condition has not yet been tried very frequently. It seems to be most beneficial in the more acute cases. Such a serum to be of value must be polyvalent. Better results have been obtained by active vaccination with killed cultures of gonococci, especially in the more chronic cases. In 1906 Cole and Meakins reported on the treatment of fifteen patients by means of vaccines, with good results. Since then this method has been quite extensively employed by numerous observers. The reported results, while not uniform, have, on the whole, been favorable. The best dosage and the proper time intervals have not been carefully worked out. Probably the best results will be obtained when the initial dose is one just large enough to produce a mild general reaction. Following this, the dosage may be gradually increased, though it is probably better that severe general reactions be avoided. In most cases an initial dose of 200,000,000 bacteria is not too large, though there is considerable difference in susceptibility in different patients, and there is also considerable variation in the toxicity of the vaccines prepared from different cultures. The doses should be repeated in from five to seven days. Good results have been reported following the injection of much smaller doses at more frequent intervals, but the writer has had no experience with this method. It is quite probable that with more accurate knowledge of the best methods of administration and the use of homologous vaccines, better results will be obtained than those seen at present.

Counter-irritation, either by the application of the Paquelin cautery or by baking, seems frequently to have a beneficial influence. In using the oven, the joint should be wrapped in flannel, and the temperature raised to 250° to 300° F. for twenty minutes; then the oven is allowed to cool before removing the extremity. Of late years passive hyperemia, introduced by Bier, has been largely employed as a therapeutic measure, with apparently good results. In applying this to the knee, a flannel bandage is first placed on the foot and lower leg. Then, a short distance above the knee, two or three turns of a thin, light rubber bandage are applied. This must not be tight enough to cause arterial obstruction.

The toes should remain warm and the skin over the knee should become flushed and hot. If it is pale and cold, the tourniquet is too tight. If it causes pain it is too tight, and should be at once readjusted. It is advised to leave it on the first time not over three or four hours, but this time may be increased from day to day, so that after a few days the bandage remains on for twelve out of the twenty-four hours, or even longer.

Whenever the joint becomes distended with fluid this should be aspirated at once. The removal of the fluid frequently gives great relief from pain, but often it quickly reaccumulates. Repeated aspiration may be performed under these circumstances. The application of a tight flannel bandage immediately after aspiration may aid in preventing reaccumulation. As soon as the most acute stages are over, passive motion should be employed, despite the pain produced.

Surgical Treatment.—The above described methods suffice in a considerable number of cases, but unfortunately, not in all, and in spite of the greatest care, some of the more severely affected joints will go on to erosion of the cartilage and bone with ankylosis, unless other measures are employed. It is to prevent this unfortunate result that recourse must frequently be had to surgical measures. Opening the joint and careful irrigation with antiseptic solutions will, in the majority of these cases, prevent the progress of the infection, and bring about rapid and complete recovery. The great difficulty is to make an early decision as to the joints which it is necessary to open. The demonstration of gonococci in the joint fluid has been considered by some to be a positive indication for arthrotomy. Certainly when gonococci are found, it is much safer to call in a surgeon, but on account of the frequent difficulty in demonstrating the presence of gonococci in the joints, even when they are present in considerable numbers, we cannot rely on this criterion alone. On the other hand, we cannot state positively that every joint from which gonococci are cultivated will go on to suppuration and ankylosis. The writer has had one patient under observation in whom gonococci were cultivated from the joint fluid; the patient refused operation and the joint recovered completely with perfect motion.

Even though gonococci are not demonstrated, however, we feel that if on aspiration a very turbid cloudy fluid is obtained, and if the local and general symptoms are quite severe, the treatment should be surgical. Also, although the fluid obtained on aspiration be quite clear, if it repeatedly reaccumulates and the symptoms and signs remain marked, it is much safer to have the joint opened.

Where ankylosis has occurred, the treatment is most difficult. If the stiffness is due only to periarticular thickening, the adhesions may occasionally be broken up under a general anesthetic, and by subsequent passive motion and massage a movable joint obtained. It may be necessary to repeat the movements under a general anesthetic on one or more occasions. There is so much pain associated with this method, and it requires such a degree of Spartan fortitude on the part of the patient to keep up the motion in such a joint, that sometimes the result is hardly worth the effort, and it is extremely rare that a patient can be induced to persist sufficiently to obtain a satisfactory result. The

method should always be tried, however. If bony ankylosis has occurred the treatment must be entirely surgical.

Results.—With the methods outlined above, and especially with early operation in the more severe cases, the results are very satisfactory. The great danger is that permanent ankylosis may result, or that the condition may become chronic.

Relation to Arthritis Deformans.—Permanent changes in the joints not infrequently follow the more severe cases of gonorrhœal arthritis. These changes may be associated with more or less persistent pain, and there may be mild exacerbations extending over considerable periods of time, even years. These features have led some writers to suggest a very close relationship between gonorrhœal arthritis and arthritis deformans, some even going so far as to suggest that gonococci may be the cause of certain cases of the latter disease. In certain cases of spondylitis deformans also there seems to be a relationship between the lesion in the spine and a gonococcus infection.

Painful Heel, Gonorrhœal Heel, Painful Foot, Talalgia.—Certain patients giving a history of an attack of urethritis, either with or without arthritis, complain of pain in the feet on walking. This pain and tenderness usually become localized in the plantar surface of the heel. The affection is usually bilateral and may run a very chronic course. The association with gonorrhœa has long been noted, and various theories in regard to the pathology have been advanced. Baer has shown that in some of these cases there is a bony outgrowth on the plantar surface of the calcaneum. In three of such cases gonococci were demonstrated, once in pure culture and twice in stained sections, thus furnishing the absolute proof of the relationship of gonococci to this condition.

Removal of the exostoses by incision on the lateral aspect of the foot may completely relieve these patients, so that surgical interference is indicated in all patients showing exostoses.

Gonococcal Bone Lesions.—Acute bone lesions, as periostitis, osteitis, and osteomyelitis, may also occur. Osteomyelitis is of very rare occurrence. These acute lesions have a more important surgical than medical interest and need not be discussed further.

Gonococcal Tenosynovitis.—This is frequently associated with arthritis, but may occur independently. The infection usually occurs in the tendon sheaths about the ankle or wrist-joints. It is best treated by fixation and the application of the Paquelin cautery.

Gonococcal Chondritis and Perichondritis occur occasionally.

Gonococcal Myositis.—Muscular Atrophy and Non-suppurative Myositis.—Associated with arthritis in almost all cases, more or less extensive atrophy of the adjacent muscles occurs. This, as is well known, is not peculiar to gonorrhœal arthritis, but occurs in association with all sorts of joint lesions. Probably in some of the cases a true non-suppurative myositis occurs in association with the joint lesion. The differentiation of nerve and muscle involvement, however, especially when there is a great deal of peri-articular infiltration and œdema, offers very great difficulty, and it is questionable whether it can be done. The occur-

rence of a non-suppurative gonorrhœal myositis unassociated with joint lesions has so far not been demonstrated.

Suppurative Myositis.—Acute inflammation of the muscles with pus formation may occur either as an extension from an infected joint, or as a local manifestation of a general infection. The former probably occurs with considerable frequency, the latter with very great rarity. The treatment in these cases is surgical, free opening, and drainage.

Gonococcal Adenitis.—Cases of adenitis with the isolation of gonococci from the infected gland have been reported. The course is not characteristic and the treatment does not differ from that employed in other forms of suppurative metastatic infection of the glands.

Complications Involving the Nervous System.—Symptoms of involvement of the nervous system occur not infrequently in association with gonorrhœal infections. The etiological relationship is not clear, however. According to some writers the lesions in the nervous system are due to the action of toxins. Many of the reported cases have undoubtedly been examples of purely accidental association of nervous lesions and gonorrhœa. A sufficient number of cases, however, have now been reported to render it quite probable either that the gonorrhœal infection favors the development of certain nervous lesions which are not strictly gonorrhœal in origin, or that the gonococcus itself, or its toxins, may induce specific nerve lesions. So far, however, no specific clinical or pathological features have been noted. The main lesions which have been described are the following:

Neuritis and Neuralgia.—During an attack of gonorrhœa there may occur either a *neuralgia* associated with paroxysmal attacks of pain in the course of the nerve trunks, or a *neuritis*, with more continuous pain, and tenderness over the nerves, with consecutive muscular atrophy and electrical reactions of degeneration. These forms of nerve involvement occur especially in association with inflammation of the adjacent joints. In many cases it is difficult to differentiate the symptoms of neuritis from those associated with the arthritis, especially where there is much muscular atrophy secondary to the joint involvement.

Sciatica.—Lesser has drawn special attention to the gonorrhœal sciatica, and thinks that many of the cases of sciatica without obvious cause, especially in women, have this origin. He points out as distinguishing features the very sudden onset during or shortly after an attack of acute urethritis, the infrequency of recurrence except with a fresh attack of urethritis, and the presence of fever.

Generalized Polyneuritis and Meningomyelitis.—Cases of general neuritis unassociated with arthritis occur with very great rarity. The association of lesions of the spinal cord with gonorrhœa has long been recognized. There are several views held as to the nature of the cord lesions occurring during gonorrhœa: (1) The early view that the symptoms are due to reflex impressions on the cord from the local lesion, the so-called "urinary paraplegia." There have been various modifications of this theory, but for none is there any evidence. (2) That a myelitis is present, originating by extension upward of a neuritis involving the nerves supplying the genito-urinary organs. (3) That a true meningo-

myelitis is present, due either to the gonorrhœal toxins or to a localization of gonococci in the cord. Leyden especially has drawn attention to the occurrence of gonorrhœal myelitis.

Neuroses.—Of more importance probably than the organic gonorrhœal nervous lesions, is the functional psychic disturbance which so often accompanies and follows the gonococcus infection, especially when this is prolonged and associated with metastatic foci. While properly not strictly part of the gonorrhœal infection, it belongs to the so-called "paragonorrhœal complications" (Jadassohn), namely, these processes in which neither the gonococcus nor its toxin may be regarded as the direct cause of the phenomena. The symptoms may be of any grade, from slight mental depression and psychoneurosis to hysteria, psychasthenia, or marked melancholia. These are not infrequently seen in patients with arthritis and form a distressing feature. They are especially marked in chronic prostatitis. In some cases, with the relief of the prostatic irritation, the mental features entirely disappear.

Pulmonary Complications.—Pneumonia.—Either lobar or lobular pneumonia may occur during an attack of gonorrhœa, and pneumonia has been present in certain cases of gonorrhœal septicemia. The pneumonia occurring under these conditions, however, shows no special features, and the absolute proof is still wanting that gonococci play a direct role in the production of this lesion.

Pulmonary infarction has occurred in cases of gonorrhœal endocarditis (case of Thayer and Lazear).

Pleurisy.—A considerable number of cases of pleurisy said to be due to gonococci have been reported. In most of these the proof is lacking. The demonstration of the etiological agent in the pleural effusion in so many cases of pleurisy, especially the tuberculous form, is attended with so much difficulty that negative cultural results afford little evidence that a pleurisy is gonococcal in origin.

Renal Complications.—Albuminuria.—This frequently occurs during the course of gonorrhœa. As Lewek has shown from a study of 155 cases, the albuminuria is usually associated with the presence of blood and pus, and has no significance as to the presence of a renal lesion. In the few cases where the amount is too large to be accounted for in this way, it may be due to a febrile albuminuria, the fever being due to the other complications usually present in such cases, or the albuminuria may be associated with irritation of the kidneys by administered drugs, such as sandal-wood oil or copaiba. In none of Lewek's 155 cases was a kidney lesion present. There is no evidence that the gonococcus or its toxin plays any role in the production of an acute or chronic non-suppurative nephritis. On the other hand, it is undoubtedly true that suppurative kidney lesions may be due to the gonococcus, either as a result of ascending infection from a cystitis, or as a focus of infection in pyemia.

Cystitis.—That gonococci alone may induce an acute cystitis has been shown by the work of Young,[1] who from such a case obtained a pure culture of gonococci in the urine by suprapubic aspiration of the

[1] *Johns Hopkins Hospital Reports*, vol. ix, p. 677.

bladder. That gonococci, however, may be present in the bladder without inducing a cystitis has also been shown by Young. A second factor, therefore, must occur in the etiology. Young has also reported a case of chronic cystitis, in which this organism was shown to be the sole bacterium present.

Peritonitis.—That a local circumscribed peritonitis may be caused by the gonococcus alone was definitely established by Wertheim in 1891, so overthrowing the view previously held that the peritoneum possesses an immunity to infection with this organism. This local peritonitis is usually associated with salpingitis, and has mainly a gynecological interest. Pelvic peritonitis occurs also in the male, and Battez has collected 30 cases. It is almost always secondary to gonorrhœal cystitis, prostatitis, or especially epididymitis and vesiculitis. There is usually intense pain in the inguinal-scrotal region radiating to the iliac fossa. It has a short duration, intense local and general symptoms, and a relatively favorable prognosis. Rectal examination is of the greatest value for diagnosis. The occurrence of a pure gonorrhœal general peritonitis, while long suspected, was only definitely established by the demonstration, by Young, of gonococci in pure culture in a case of general peritonitis occurring in the Johns Hopkins Hospital in 1898.

The condition occurs principally in young girls, or in women during or just after menstruation, or during the puerperium. In all cases so far reported, the infection has apparently reached the peritoneum by ascending through the Fallopian tubes. The onset of the symptoms is usually quite acute and the features are those of the other forms of general peritonitis. While these symptoms *may* be of great severity, they frequently are milder than are seen in the other forms of peritonitis, except in the tuberculous form. The collapse is usually not so extreme, and frequently after three or four days of marked symptoms of general peritonitis the condition improves. There are no definite clinical features, however, by which this form of peritonitis may be differentiated from the more severe forms caused by the pyogenic cocci. Symptoms of general peritonitis coming on suddenly in a young child or in a woman during the puerperium or just after menstruation, especially if the presence of an infection with gonococci at the same time can be demonstrated by the isolation of these organisms from a urethral, vaginal, or cervical discharge, make the diagnosis very probable. This is still more probable if, on pelvic examination, salpingitis is found.

Prognosis and Treatment.—Of 39 cases collected by Hunner and Harris, 27 recovered, 12 died, and of the 27 recovering, 8 received only palliative and medical treatment. Until the clinical features are better known and the means of diagnosis more certain, treatment should be surgical, or at any rate the surgeon should be permitted to take the responsibility of delaying operation.

Metastatic Ocular Complications.—Aside from the primary ocular gonococcus infections, certain other eye lesions may occur, which are manifestly metastatic in origin, and represent either the effect of the gonococcus toxin upon the eye, or are true local manifestations of a general gonococcal infection.

Metastatic Conjunctivitis.—There has been much discussion as to whether such a condition really occurs, but from a study of the reported cases it seems probable that a conjunctivitis sometimes occurs during gonorrhœa, in which a direct transplantation of the virus from without can be excluded. A considerable number of cases have been reported, though the condition is relatively infrequent. It seems to have certain special features. The symptoms are much milder than those occurring in the ordinary form of conjunctivitis, and the course is much shorter, there being a tendency to spontaneous recovery in from six to fourteen days. Both eyes are affected, and the condition is usually accompanied by other metastatic lesions, frequently arthritis and iritis. The treatment consists in mild antiseptic washes and absolute rest for the eyes.

Metastatic Iritis.—This condition is of special interest, as it usually occurs in association with arthritis. It may occur either as the so-called spongy iritis, or any of the various forms of plastic iritis, and even the hemorrhagic form has been described. Only one eye may be affected, or both may be attacked, simultaneously or in succession. A tendency to recurrence during subsequent attacks of gonorrhœa has been observed. Practitioners should look on any eye symptom occurring during the course of gonorrhœa with suspicion, otherwise this condition may be overlooked, and when discovered the damage be irreparable.

Mydriatics should be used as soon as possible to prevent adhesions leading to closure of the pupil. Usually the course is mild, and when properly treated, complete recovery is the rule. The treatment is exactly the same as that employed in other forms of iritis.

Dacryo-adenitis.—Cases of so-called metastatic gonococcal inflammation of the lacrymal gland have been reported. Other forms of metastatic eye lesions have been recorded, as tenonitis, keratitis, iridocyclitis, iridochoroiditis, retinitis, neuroretinitis, and optic neuritis. The exact relationship of these lesions to the gonococcal infection is not yet clear.

Gonorrhœal Skin Eruptions.—The occasional occurrence of skin eruptions during the course of gonorrhœa, especially the association with extragenital complications, has long been noted. The relationship of these to the gonorrhœal infection has not been clear, and even now definite proof of an etiological relationship is wanting. Buschke,[1] who has made a study of these lesions, divides them into four groups:

1. **Simple Erythema.**—This is the most frequent form, but in many cases is often but a sequel of certain forms of treatment. It may occur, however, in conjunction with gonococcus septicemia.

2. **Urticaria and Erythema Nodosum.**—Certain of the cases have shown exactly the lesions of erythema nodosum, with raised tender nodes and deep infiltration of the subcutaneous tissue. In most of them there have been joint pains, in some a typical gonorrhœal arthritis.

3. **Hemorrhagic and Bullous Eruptions.**—Such lesions have usually appeared in cases with the manifestations of a severe septicemia, and they are probably (as is quite certainly the case in other infections such as streptococcus) embolic in origin.

[1] *Arch. f. Dermat. u. Syph.*, Wien, 1899, xlviii, p. 181.

4. **Hyperkeratosis.**—This is by far the most interesting group, as the lesions are apparently specific. These lesions and the clinical features have been more extensively described by Baermann. This lesion is undoubtedly rare, though possibly cases are overlooked. The skin eruption usually follows a severe general infection, usually associated with joint lesions. Owing to this, emaciation and anemia occur. Then suddenly, on the plantar surface of the feet, palmar surface of the hands, or about the nails, an eruption appears. This may remain localized or become widely distributed over the body. The eruption consists of scaly efflorescences on an entirely re-actionless base. After these fall off, no scar remains. On the hands and feet the eruption may be diffuse and confluent. Often the extremity most involved is the one in which the joint lesions are most marked. With recovery from the joint lesions and other gonorrhœal manifestations, the skin lesion heals of itself. Gonococci have not been found in these local lesions, and the association with the gonorrhœal infection is not clear. The French writers consider the condition a trophoneurosis, due to toxic changes in the nerve endings. Baermann does not think the crust formation is a true keratosis, but thinks the term *dermatitis papillaris parakeratotica* is better. The condition must be diagnosed from a luetic eruption and from psoriasis. Roth also does not consider the condition a true keratosis, but considers that it belongs among the "angiopathic" skin eruptions.

Gonococcus Infections in Children.—This is of great importance, not only to the pediatrician and genito-urinary surgeon, but to the general practitioner as well. While of greatest importance in connection with the care of children in hospitals, in which the epidemic occurrence of this infection renders it a most difficult and important problem, it probably occurs in private practice with much greater frequency than recognized or hitherto imagined. The studies of Holt and Reed from institutions for babies in New York, show that this condition is almost constantly present in practically all of these institutions. During eleven years, in the Babies' Hospital, New York, 273 cases occurred, of which 172 were undoubtedly acquired in the hospital. The disease is almost entirely confined to females, as during this time there was only 1 case of gonococcus urethritis in a male child. The usual mode of spread in these young children is through the medium of napkins, by the use of baths, or by the use of infected thermometers, syringes, and possibly tongue depressors.

The recurrence of this infection in hospitals can only be prevented by the exclusion of infected children, and this can only be done by the systematic microscopic examination of the vaginal secretion of all patients applying for admission, and by the rigid isolation of all children in whom infection develops, or is only discovered after the child is admitted. Some of the cases are very mild and without bacteriological examination are easily overlooked. The importance of this infection is dependent not only on the local infection induced, but on the complications which are liable to occur. Endometritis, salpingitis, oöphoritis, and peritonitis, frequently leading to sterility, are not very infrequent occurrences. Metastatic foci also occur with considerable frequency.

CHAPTER XXI

BACILLARY DYSENTERY

By K. SHIGA, M.D.

Introduction.—Until recently it was customary to divide dysentery into three forms, epidemic, endemic, and sporadic; or to separate it, according to the clinical features, into two main groups, acute (catarrhal, fibrinous, or diphtheritic) and chronic or tropical dysentery. Since the discovery of the dysentery bacillus new light has been thrown upon the disease, and it may be divided into two forms, bacillary and amœbic.

Bacillary dysentery is an infectious disease produced by the *B. dysenteriæ*. Pathologically it produces catarrhal and diphtheritic inflammation, with the formation of necrotic ulcers in the intestine. Clinically it is characterized by frequent slimy and bloody stools accompanied by tormina and tenesmus. In 1898 Shiga found the *B. dysenteriæ* in the epidemic dysentery in Japan, and in 1900 Flexner, Strong, and Musgrave studied cases of dysentery in the Philippines and isolated a bacillus which corresponds in all marked points with that of Shiga. Almost simultaneously with the papers of Flexner, Kruse (1900) published his investigation on an epidemic of dysentery in Germany and found a bacillus corresponding with that of Shiga. Thereafter the bacillus was found and confirmed by many observers in different parts of the world. In cases of summer diarrhœa in infants in the United States the dysentery bacillus was found by Duval and Basset, by Knox, and Woolstein. In 1903 the study of this disease was especially undertaken by Flexner and Holt, and it became apparent that the dysentery bacillus can cause infantile diarrhœa in both summer and winter. In Japan, Ohno, an assistant in Kitasato's Institute, has confirmed the presence of the bacillus in summer and winter diarrhœa. In the Russo-Japanese war the bacillus was found in dysentery in Manchuria, among the Russian troops at Port Arthur, and in Korea.

Bacillus Dysenteriæ.—Dysenteric bacilli are small plump rods with rounded ends, very similar to colon bacilli. They are usually single, but occasionally occur in pairs. They are not motile,[1] and no flagella can be demonstrated. There is no spore formation. The bacillus stains readily with the ordinary aniline dyes, but is decolorized by Gram's method. The bacillus grows well on the usual culture media. Gelatin is not liquified, nor indol produced.

Gelatin Plates.—Deep colonies are round or oval and possess sharp borders. Surface colonies are often, but not constantly, leaf-like in appearance, like the colonies of typhoid bacilli.

[1] In the first investigations I described the bacillus as being slightly motile. Kruse described his bacillus as non-motile, and now his view is accepted universally.

Agar Culture.—Like the typhoid bacillus they show less growth than the colon bacillus. After twenty-four hours they form small, thin colonies which are round and have a moist appearance when viewed obliquely. After several days they become thicker, of a grayish-white color, and show thread formation. The agar culture is remarkable for a sperm-like odor. *Glucose-agar* shows grayish-white growth along the entire line of inoculation, but has no gas formation.

Bouillon shows even clouding with sedimentation, but after standing for a time the upper part becomes clearer.

Litmus milk gives weak acid formation after one to three days and after five to seven days an alkaline reaction and a gradual increase in the blue color of the culture.

Potato.—The development is different according to the reaction of potato used. If the potato is acid, the growth is not perceptible by the naked eye. It is, however, apparent and brownish or white in color if the potato is cooked in a soda or salt solution, and is alkaline or neutral in reaction.

Involution Forms.—When *B. dysenteriæ* is cultivated upon agar which contains a large percentage of salt, various involution forms are seen. Upon 5 per cent. NaCl-agar such forms are especially prominent, and appear in very irregular shapes. Hata showed that involution forms become specific and more prominent upon $\frac{3}{4}$ per cent. calcium agar.

Animal Experiments.—The injection of a small quantity of dysentery bacillus culture into the peritoneal cavity of guinea-pigs causes a mucous, often a bloody diarrhœa; the animal dies in a few days. The peritoneum is markedly injected, and in the peritoneal cavity there is an abundant bloody exudation. The contents of the intestine are slimy and in the walls of the cecum severe hyperemia and hemorrhages often occur. Among animals this result is most marked in rabbits. The injection of even a small amount of the bacilli causes severe catarrh and hemorrhages upon the serous membrane and the walls of the bowels, with paralysis of the limbs and death of the rabbit after some days. The author succeeded in causing a dysenteric lesion in the walls of the bowels (cecum), just as in a human body, by injecting a small quantity of dysenteric bacilli.

The Soluble Toxin.—The action of the dysentery bacillus toxin is very characteristic, and rabbits are very sensitive to it. When 0.1 cc. or less of the filtrate of a seven-days' bouillon culture is injected intravenously it causes the death of a rabbit in twenty-four-hours; at autopsy remarkable hyperemia and hemorrhages upon the serous membranes and the walls of bowel are visible, just as with a living culture. A similar action is also produced with the filtrate of a twenty-four-hour agar culture heated at 60° C. for one hour and diluted with normal saline solution (Neisser and Shiga). The toxin which Conradi has obtained with autolysis is also identical with the toxin above mentioned. The soluble toxin consists of two components: (1) a nerve toxin which produces paralyses in the limbs and urinary bladder with severe hemorrhages in the cord, and (2) enteric toxin which causes the dysenteric changes in the bowels (especially the cecum).

These toxins, obtained by different methods, are qualitatively identical; the animal experiment shows this accurately, and we can also prove it by the action with immune serum (Todd, Rosenthal). Heating at 70° C. for an hour has no influence upon this toxin; even its exposure to 80° C. does not seem to destroy it entirely, although it is affected slightly at 75° C.

The Types of Bacillus Dysenteriæ.—It was Kruse who first paid attention to the difference of serum reaction between the bacillus and Shiga-Kruse and that of Flexner (Manila type). In this investigation he described a so-called "pseudodysenteric bacillus" found in the stools of insane patients suffering from a form of dysentery and in material from autopsies. This organism he could not distinguish morphologically nor culturally from the dysenteric bacillus, but it differed in the serum reactions. Spronck isolated an organism in Utrecht which differs from the Shiga-Kruse organism in the agglutination reaction, and apparently belongs to the same group as Kruse's pseudodysentery bacillus; but its etiological significance is probably established.

The committee for the investigation of *B. dysenteriæ* (Koch, Pfuhl, Schmiedecke, v. Drigalski, and Jürgens) studied carefully the Shiga, Kruse, Flexner, and Döberitz bacilli, and found that the Flexner type differs from the others in its agglutination reaction with the patient's serum. Shiga[1] compared the action of the immune serum on the Shiga and Kruse organism and found that they are identical from the agglutination and bactericidal standpoints. He showed that there is a difference in receptor apparatus between the bacillus of Shiga-Kruse and that of Flexner. When the immune serum is saturated with a Shiga culture, all the agglutinins and pro-agglutinoids for Kruse's organism are absorbed by the bacilli; and when these are removed with centrifugalization, the serum is no longer able to agglutinate fresh additions of Shiga-Kruse bacilli, while its limit for the Flexner bacillus is only slightly changed, or *vice versa*.

Martini and Lentz[2] showed with immune sera that the Manila bacillus of Flexner and Strong differs from that of Shiga and Kruse. Lentz[3] could show this differentiation also on the mannite agar culture. The principal difference was that the Shiga-Kruse bacilli did not affect mannite (non-acid form) while the Flexner and Strong cultures fermented mannite (acid form), giving rise to a distinct acid reaction in the medium. Hiss and Russel[4] described a bacillus (B. "Y") from a case of fatal diarrhœa in a child, and found that this bacillus differed from the Kruse cultures in its ability to ferment mannite. Hiss distinguished at least three groups among the bacilli isolated from dysentery or diarrhœa cases, cultivating these in the medium of mannite, dextrose, maltose saccharose, and dextrin. One group represented by the Shiga-Kruse culture fermenting monosaccharides only; one of the Hiss and Russel

[1] "Weitere Studien über den Dysenteriebac," *Zeitschr. f. Hyg.*, 1902.
[2] "Ueber die Differ. der Ruhrbaz mittels der Agglut.," *Zeitschr. f. Hyg.*, 1902.
[3] "Vergleich. Cultur. Untersüber die Ruhrbaz.," etc., *ibid.*, 1902.
[4] *The Medical News*, 1903. This observation was made independently of Lentz's work.

culture fermenting monosaccharides and mannite; and finally a group represented by the Flexner culture fermenting monosaccharide, mannite, maltose, saccharose, and dextrin.

Gay studied the types of dysentery bacilli in relation to the bacteriolysis and preventive power of sera. He concluded that "the dysentery bacilli fall into two types, according to certain cultural and agglutinating reactions; but these reactions are not absolute, but relative, and serve to give the bacilli the characters of a closely related group of organisms. Bacteriolytic differences serve to distinguish the two types of dysentery bacilli, now recognized as sharply as the other tests hitherto employed." Park, Collins, and Goodwin[1] divide the dysentery bacilli into three types: (1) No production of indol; does not ferment mannite, maltose, nor saccharose (Shiga bacillus); (2) ferments mannite, but does not split maltose or saccharose, produces indol, and (3) produces indol and actively ferments mannite, also acts energetically upon pure maltose and feebly upon saccharose.

It is obvious that there are many different types of dysentery bacilli, and each of these can be the etiological factor in dysentery. As to the classification of these bacilli; Hiss[2] studied this question and divided them according to their fermentative action upon monosaccharide (dextrose), disaccharides (maltose and saccharose), polysaccharide (dextrin), and the mannite, with which the agglutination reaction and the absorption tests agree. The groups are divided as follows: The first group ferments only monosaccharide (Shiga, Kruse, New Haven bacillus). The second group ferments monosaccharide and mannite ("Y," Ferra, Seal Harbor bacillus). The third group ferments monosaccharide, saccharose, and mannite (Strong's bacillus). The fourth group ferments monosaccharide, mannite, maltose, saccharose, and dextrin (Harris, Gray, Baltimore, Wollstein bacillus). In the epidemic of dysentery in Japan, 1904, we collected at the institute in Tokio many types of dysentery bacilli from several parts of Japan and studied their differences. We have found a new type which ferments dextrose, mannite, saccharose, maltose, and dextrin as the fourth group of Hiss, but differs from it in returning to an alkaline reaction after four or six days. The agglutination test of this type showed a wide difference from the others, so that this bacillus should be placed in a new type. The bacteriolytic as well as the agglutinative action of immune sera of our four types differ also from each other. The high virulent toxin action on rabbits exists only in the first type (Shiga), but not in the others.

As to the relation of those types to the pathology, symptomatology, and epidemiology, Flexner and Holt[3] make no difference in the clinical features of the summer diarrhœas of infants caused by the mannite fermenting and non-fermenting organisms. The Shiga bacillus and Flexner-Harris bacillus (the mannite fermenting organism) often exist in the same patient. Thus Gay and Duval[4] reported 3 cases in acute

[1] *Journal of Medical Research*, 1904, vol. xi, No. 2.
[2] Ibid., vol. xiii, No. 1.
[3] *Studies from the Rockefeller Institute*, 1904, vol. ii.
[4] *University of Pennsylvania Medical Bulletin*, 1902, vol. xvi.

adult dysentery, Hastings[1] 2 cases, and Duval and Shorer[2] 6 cases in the diarrhœal diseases of infancy. It must also be mentioned that the frequency of occurrence of each type differs according to year, season, place, and epidemic. Thus in the epidemic of dysentery in Tokio, 1904, we confirmed the presence of bacilli belonging to the first type in but a few cases, but those belonging to the third and fifth type in a large number, while a greater number of cases in Kobe in Japan, in Manchuria, and among the Russian troops in Port Arthur, was caused by the first type and only a few cases by the other types (mannite fermenting bacilli).

Infection and Epidemiology.—The most important source of infection is the individual suffering from dysentery. The organisms occur in the stools in innumerable numbers, and through carelessness the clothes of the patient and also other articles are soiled and the bacilli thus carried from one person to another. In this way we find contact infection in a large number of cases in every dysentery epidemic.

Then, too, the dysentery bacilli are often carried with the dejecta into rivers and other water supplies and cause infection through drinking-water. In a village called Momma-Mura, at Nobechi, in Japan, in 1900, a dysentery epidemic broke out and it was proved that the well, used by all the households suffering from the disease, was infected with the dysentery bacillus. We have also an interesting example of river-water infection in Japan. There is a village called Mitake-Mura in the district Miyagi-Ken, through which a river flows. Fishing and swimming are prohibited in it because of fish-breeding. In the late summer of 1889, the prohibition having been removed, the men of the village were allowed to fish and swim in the river and after four or five days an epidemic of dysentery broke out, with 10 patients on the first day and increasing numbers daily afterward. There were in all 413 cases, of which 115 were boys under ten years of age. It was found that there was an epidemic of dysentery in a village higher up the river, and the water had been soiled by the infected clothes.

The transportation and handling of milk or other kinds of foods may also be a cause of an epidemic of dysentery, and, indeed, sometimes a common bath-house may be a cause of infection. We had such an instance in Kobe in Japan. It is probable that the fly has some part in the transmission of the disease, for having settled on the dejecta of a dysentery patient it can carry the germs of the disease and deposit them directly upon food or even in the mouth.

As in other epidemic diseases, dysentery prevails especially among people who live in unhygienic surroundings. It always accompanies war. In the Japanese-Chinese war (1894–1895) we had 10,681 patients (of whom 1157 died, or 12.7 per cent.), the number of patients being about 10 per cent. of all diseases, and, indeed, $3\frac{1}{2}$ times more than the wounded.

The severity of the epidemics differs, as is shown by the mortality. In the whole of Japan this varies every year between 22 and 26 per cent. of

[1] *Studies from the Rockefeller Institute*, 1904, vol. ii.
[2] Ibid.

cases.[1] According to Kruse,[2] the mortality in Germany is 10 per cent., in Russia it amounts to 17.5 to 12.2 per cent. (Rosenthal[3]). According to Manson,[4] the mortality from dysentery among Europeans in India ranges from 3 to 22 per cent., among the natives about 36 to 40 per cent.

Age and Season.—Young men from twenty to thirty years of age often suffer from dysentery, perhaps because of frequent exposure. Epidemics prevail from the early summer (June or July) until the late autumn (October). Through winter there are only a few cases and in some parts of the country it disappears entirely, to reappear in the next year. We can therefore suppose that the dysentery bacilli exist through the winter in a human subject, who either seems perfectly healthy, or suffers only from slight diarrhœa. We really have such cases. Ohno has found the bacillus in the stools of an apparently healthy man living near a household in which there was an epidemic of winter diarrhœa. Wollstein[5] found the bacillus at autopsy in 3 infants who had no symptoms of dysentery or summer diarrhœa, the bowels showing only a slight catarrh. She aptly says: "*B. dysenteriæ* may be present in the intestinal mucosa in cases of a very mild catarrhal inflammation of the colon, either as a terminal infection or as the remains of a previously active infection when clinical manifestations do not warrant the diagnosis of dysentery." Conradi[6] found the dysentery bacillus in the apparently normal dejecta of 5 healthy infants aged two and one-half to eleven years, whose sisters and parents at that time suffered from dysentery. During an epidemic of summer diarrhœa, Duval and Shorer[7] succeeded in isolating a few colonies of the Flexner-Harris bacillus from the stools of two infants who were in perfect health.

It is interesting to know how long after convalescence the dysentery bacillus exists in the stools of patients. We can, *a priori*, suppose that, as in typhoid, the bacillus can be found long after recovery. It was lately stated by Momose, in Japan, that the dysentery bacillus disappears from the stools of convalescents after thirteen to fifteen days. But there are exceptions, for the bacillus may be found in the stools a month after without any intestinal disturbance. V. Drigalski reported relapses occurring at intervals and also instances of relapse in soldiers after their arrival in Germany from China. Lentz reports the case of a soldier, who, after recovery from dysentery, left his regiment and was the source of a dysentery epidemic after his return to his native village. According to the results of investigations by Ohno with myself, the persistence of bacilli in the stools depends upon the severity of the attack; the lighter this is the sooner the bacilli disappear, even after five days; but the more severe the attack the longer the bacilli persist, even to the nineteenth day after convalescence. Patients either with no symptoms or slight ones only, and convalescents who have been discharged from the hospital

[1] Shiga, *Deutsch. med. Woch.*, 1901.
[2] *Centralbl. f. allgem. Gesundh.*, 1900.
[3] *Deutsch. med. Woch.*, 1904, No. 19.
[4] *Tropical Diseases*, 1903.
[5] *Studies from the Rockefeller Institute*, 1904, vol. ii.
[6] *Festschr. zum 60 ten Geburtstage von R. Koch.*, 1903.
[7] *Studies from Rockefeller Institute*, 1904, vol. ii.

but have dysentery bacilli in their stools, are often the cause of fresh epidemics in places where dysentery has not been for a long time.

Pathological Anatomy.—The lesions are those of a diphtheritic catarrh of the bowels. The large bowel is usually the seat of the disease, but it affects the cecum and part of the ileum not infrequently. The dysentery bacilli remain in the folds of the intestine and multiply under favorable conditions, among which may be mentioned constipation and intestinal disturbances. The mucous membrane reacts by inflammation which may be catarrhal, hemorrhagic, or diphtheritic, according to the stage and grade of the process. The diphtheritic infiltrated mucous membrane becomes necrotic, and thus ulcers are produced. The elevated parts of the mucous membrane, the folds, are most affected, and from these the process spreads later to the surrounding parts.

In the beginning of the catarrhal period, the surface of the mucous membrane has a grayish-red, velvet-like appearance. The mucous membrane becomes red and swollen in consequence of hyperemia and catarrhal œdema. This is succeeded in the second period by necrosis of the epithelium, which is noticeable macroscopically by the presence of flecks, which microscopically are nothing but the groups of epithelial cells, the nuclei of which are hardly stained. Gradually the necrosis proceeds in the deeper parts and the whole wall of the bowel now appears thickened. The lymph follicles of the mucous membrane become necrotic and purulent and with the sloughing of these as the third period of the disease appears, comes the formation of ulcers. In contradistinction to the undermined ulcers of amœbic dysentery, which increase deep in the mucous membrane, the ulcers in epidemic dysentery are accompanied usually with only the damage of flat layers with irregular borders. The formation of the ulcers proceeds deep in the submucous and to the muscular layer, often leaving the muscular layer bare. The border of the ulcers is reddened, swollen, and infiltrated.

In the small intestine the mucous surface throughout may be normal, or more commonly the mucosa in the lower portion of the ileum is more or less reddened. In the period of so-called "enterodysentery" the ileum presents in general the same reddened hemorrhagic appearance, is covered with a necrotic mucous layer and œdematous swelling as in the large bowel. The Peyer's patches are only moderately swollen or not at all; the solitary follicles may be swollen, raised, and hemorrhagic. Osler remarked that in very acute forms, as in children, the picture is that of an acute follicular colitis. According to Howland,[1] the summer diarrhœa of infants in the United States is accompanied anatomically with various features, either with pseudomembranous or follicular catarrh, superficial necrosis, and ulceration in the mucous membrane, or even only slight erosion.

The peritoneum is also inflamed, and adhesions frequently exist. Ecchymosis is present on the serous membranes in severe cases. If the lesions of the small intestine or cecum are suitably localized the corresponding mesenteric glands become swollen and show slight hyperemia,

[1] *Studies from the Rockefeller Institute*, 1904, vol. ii.

as in typhoid fever. Strong remarks that the group running toward the head of the pancreas seems particularly likely to be involved. The kidneys often show injection of the surface vessels and cloudy swelling. The spleen is not enlarged and shows no constant pathological change. The liver generally is neither hyperemic nor swollen.

The dysentery bacillus probably does not enter the general circulation. That such is the case is apparent from the fact that dysentery is never complicated by roseola, pneumonia, osteomyelitis, or the so-called infectious spleen, as in typhoid fever. The case of septicemia mentioned by Rosenthal, in which he found the dysentery bacillus in the heart blood, in pericardial hemorrhages, and in the spleen and mesenteric glands at autopsy only nine hours after death, is an exception. Markwald reported an interesting case relating to the blood infection of the fetus. The mother had dysentery and aborted in the sixth month. The child died in a few hours. The dysentery bacillus was found in its intestinal contents and also in small numbers in the heart blood. Parotitis is occasionally seen as a complication, but its connection with the dysentery bacillus is not clear, inasmuch as it may result from a secondary infection by other organisms present in the mouth.[1]

The pathological changes in the intestine predominate in the mucosa and submucosa. In the catarrhal period we can observe microscopically the bloodvessels of the mucosa and submucosa dilated and filled with blood. In the dilated lymph spaces, groups of leukocytes are visible. In the early periods the mucous membrane shows a coagulation necrosis with a fibrinous exudate and polymorphous cells. The submucosa is usually very much thickened. In certain parts of the submucosa, especially in the deeper layers, there is a marked cell infiltration. The borders of the ulcers are infiltrated and the surrounding tissue also shows a small cell infiltration.

Numerous bacteria are found in the inflamed mucous membrane and are especially numerous in the necrotic portions. They are usually bacilli, but cocci are also found. In the deeper layers the bacilli are found in small numbers; but in the glands, between the gland cells, and in the glandular stroma, they are very numerous. Cocci are not found in these locations. In the submucosa, and often in the muscularis, the cell infiltration is accompanied by the presence of numerous bacilli. Those seen in the deeper layers of the intestinal wall cannot be differentiated morphologically as the *B. dysenteriæ*, but transplantations from these regions show the presence of that organism in pure culture.[2]

General Symptoms.—Bacillary dysentery is a disease usually of acute course. The incubation period is generally two or three days, but cases are reported in which it was from three to eight days. In a case reported by Lemoine, in which infection took place by the rectum from the use of a chamber containing dysenteric stools, the incubation was twenty-four hours. Cases of infection in the laboratory which were observed by Flexner, Strong, and Kruse showed an incubation of twenty-four

[1] Shiga, *Deutsch. med. Woch.*, 1901, No. 48.
[2] Ibid., No. 43.

to forty-eight hours. In the epidemic caused by river water which occurred in a village in Japan the incubation was in most cases from four to five days.

Dysentery begins with diarrhœa and colic. At the onset the stools are of the ordinary diarrhœal character, or contain only small quantities of mucus. There is lack of appetite, weakness, and a feeling of pressure over the abdomen. Abdominal pains and tenesmus soon develop. As a rule, on the second or third day the stools become slimy and bloody in character, and very soon only pure mucus and blood are passed. The stools then have a typical appearance and a characteristic spermic odor. The quantity passed is small, usually only a half or one ounce. In severe cases the stools contain pus and rarely shreds of mucous membrane. When the bowel wall is widely affected and hyperemia and inflammation exist, the "meat-water" stools may be passed. The dirty brown stools are often mixed with gangrenous tissue. Tenesmus is very marked, and so intense that the rectum frequently becomes prolapsed and fecal incontinence supervenes. This occurs often in infants.

The body temperature in severe cases rises generally to between 101° and 102° F.; not infrequently it exceeds 104° F. The urine is decreased in amount and tenesmus of the bladder is caused.

The quantity of food ingested is diminished, the appetite often disappearing entirely. The tongue is moist and somewhat coated in slight attacks. In the gangrenous or "typhoid" dysentery, when the outlook is serious, there is a thick and dirty brown coating to the tongue, which may be dry. In chronic dysentery the tongue seems atrophic, reddened, and bleeds easily. Thirst is rarely present in the lighter cases, but in severe ones it is usually marked. The patient grows weak very rapidly, not only from the want of food, and restlessness, but also as a consequence the action of the toxin of the dysentery bacilli. Nausea and vomiting are also often associated. When the patient has retching but vomits nothing there is usually epigastric pain.

The pulse is in most cases accelerated and in serious cases small and irregular. The abdomen is usually somewhat excavated and tender on pressure. The infiltrated intestine can be plainly felt through the abdominal wall, this giving the patient great pain. The sensorium is usually clear. The patient complains often of headache and sleeplessness. Delirium is present rarely and only as a terminal symptom.

Death occurs in serious cases usually after two to three weeks, unless there is some complication to hasten it.

The general symptoms are due to the absorption of the toxins of the bacilli (endotoxin) in the body. In mild cases fever and general indisposition are absent, but they are never-failing symptoms in serious cases and those of middle grade. That the general symptoms are not so prominent as in typhoid fever is to be ascribed to the localization of the lesions. If lesions are present in the upper portion of the large intestine or in the small intestine, various intoxication symptoms appear, such as fever, headache, general malaise, muscular pains, epigastric oppression, sleeplessness, numbness, stupor, delirium, etc. If such symptoms are present it was customary to speak of "typhoid dysentery." The rapid

emaciation observed is not to be exclusively ascribed to the diarrhœa and inanition, but is partly due to the intoxication. Ecchymoses are frequently present upon the epigastrium, chest, or inner surface of the upper and lower extremities, and in the later and severe stages.

The intestinal lesions are principally located at the flexures of the colon. This is due to the fact that the mucous membrane in such locations is extremely susceptible to mechanical irritation, and hence is especially suitable for the development of dysenteric bacilli. The involvement of the lower portion of the small intestine is usually secondary, but it is very probable that primary lesions in this location do occur. As in typhoid fever, the usual seat of the lesion in the small intestine is the lower portion of the ileum. The ileocecal valve is frequently affected, being ulcerated and sometimes entirely destroyed. As a rule, the cecum and ileocecal valve are extensively diseased; the intestines above are progressively less and less involved. The histological changes in the small intestine are entirely similar to those described above for the large intestine. Many mesenteric glands are enlarged and merely hyperemic, as in typhoid fever. Following the healing of the ulcers the lumen of the intestine is narrowed by cicatrization. This is "entero-dysentery," which is thus named to separate it from "colodysentery," in which the lesions are localized in the large intestine and rectum.

The symptoms of *enterodysentery* are somewhat different from those of colodysentery. In the former, tenesmus is absent and the stools are not so frequent, but very voluminous; mucus and blood are closely mixed with the stools. No incontinence of feces is present. Tenesmus is always a sign that the rectum is involved. In distinction from colodysentery, in enterodysentery the toxic symptoms which have been described above in connection with the so-called typhoid dysentery are very prominent. The prognosis in enterodysentery is always serious. It is evident that the differentiation between entero- and colodysentery is very important on pathological, clinical, therapeutic, and prognostic grounds.

There is no doubt that the lesions can arise primarily in various portions of the small and large intestine when suitable conditions are present. When the primary lesion is in the ileum or upper portion of the large intestine and the process advances downward, it is called "descending dysentery" in contradistinction to "ascending dysentery," in which the reverse is the case and the primary lesion is situated in the lower portion of the large intestine, the process extending upward. The latter form is that usually met with. The author has noted a case of descending dysentery in a nurse, who was carefully observed from the onset, in consequence of her presence in the hospital. The lower portion of the ileum and the cecum were first attacked. She had, therefore, from the beginning a higher temperature and complained especially of general weakness and headache. The patient was restless and complained of sleeplessness. She had pain in the umbilical region, especially marked on pressure in the right iliac fossa. The ascending, transverse, and descending colon was entirely free at the beginning. Slimy stools with large amounts of blood were passed about nine times during the first day. No tenesmus was present. After a time the disease proceeded

gradually to the lower portion of the bowel, from the cecum to the colon ascendens, transversus and at the end to the upper part of the colon descendens; the progress was accurately proved by the pains on pressure. Under treatment with calomel and serum injections the process was stopped and after three weeks she was in normal health.

Chronic Dysentery.—Under this term is included the dysenteric disease in which the catarrhal symptoms have disappeared. With the feces are mixed mucus and material secreted from the areas of ulceration, and excreted only attached to the feces without being mixed through them. The process is very chronic and extensive, and we may have stricture of the bowel. The condition is, in the writer's opinion, only a subsequent disease, in which we cannot find the dysenteric bacillus or amœbæ.

Summer Diarrhœa in Infants.—The so-called summer diarrhœa in infants, which prevails in the United States every summer in large cities, especially in the warm parts of the country, is in the majority of the cases caused by the *B. dysenteriæ*—the most by acid bacilli, in a few cases by non-acid bacilli (namely, non-fermenting mannite bacilli). This disease is characterized by much mucus and generally blood in the stools, usually with fever, which is always high, and by marked general prostration. We meet very rarely the severe acute intestinal intoxication called "cholera infantum" with its sudden violent onset, protracted vomiting, high temperature, frequent serous discharges, great prostration, early collapse, and often early death. In Japan, especially in the southern parts, there are also acute infantile diarrhœas, called "ekiri," in the season of dysentery epidemics. Ohno proved in an epidemic in Tokio that the disease was nothing but dysentery in most cases, in which, however, the intoxication symptoms are very serious and found the dysentery bacilli in the stools of the patients in 65 per cent. The clinical features were almost similar to those prevailing in the United States.

The Course.—The duration is four to eight days in the light cases and three to six weeks in the serious ones. According to the author's experience the duration, on an average, was forty days under medicinal treatment and twenty-five days under serum treatment. The onset in the light cases is tolerably prompt; in severe cases, on the contrary, it is rather gradual over some weeks. In the chronic dysentery the secretion of matter and mucus is obstinate, and continues for a long period after the other symptoms have disappeared. Relapse is seen not infrequently; but in most of these cases, the disease is of a chronic nature and characterized by irregularity in the movements of the bowels, or light diarrhœa, which becomes serious again, after various indiscretions, such as overexertion.

Complication and Sequelæ.—*Parotitis* occurs often in severe cases, and also in moderate cases which run a chronic course. It is usually bilateral and appears during the third to the fifth week of the disease. Unilateral parotitis is rarely seen. Among 436 cases of dysentery the author saw only 8 cases of parotitis. The dysentery bacillus was never found in the pus and tissues removed.

Ascites is often seen in debilitated patients or during convalescence, and is frequently combined with general dropsy. *Peritonitis* occurs

somewhat often in the course of dysentery. *Beriberi* (*Kakke*) is also often observed as a complication in Japan. The prognosis is not good.

Abscess.—The author has seen only 2 cases during convalescence. In the first the upper portion of the rectus abdominalis, and in the second case the gluteal region, was affected. No one has ever observed abscess of the liver in bacillary dysentery.

Inflammation of articulations and tendon sheaths has occurred, which is to be regarded as the general result of toxemia.

Lately, Iwasaki, in Japan, reported a case of mixed infection of dysentery and typhoid fever, from the stools of which he cultivated the bacillus of dysentery and also that of typhoid. At autopsy typhoid ulcers were found at the lower part of the ileum and dysenteric ulcers in the whole of the rectum. Woodward mentions that the same combination was exceedingly frequent during the American Civil War, but in ordinary practice this is very rare. Eight similar cases are reported by the Eastern Asia Expedition Corps. Because in tropical and subtropical regions both bacillary and amœbic dysentery are simultaneously present, we can, *a priori*, expect mixed infections. As rare complications, Markwald reported acute conjunctivitis, iridocyclitis, and prostatitis.

Diagnosis.—This is usually very easy, especially in epidemics. We must regard the characteristics of the stools, colic, tormina, tenesmus, resistance over or swelling of the large bowel, and pain on pressure. We must remember that tenesmus is not a constant symptom because it exists only when the rectum is affected. The diagnosis of the abortive form of dysentery, which occurs often in winter or in the beginning of epidemics, is very difficult. Similarly, too, the diagnosis of entero-dysentery, or the so-called typhoid dysentery, is not easy. The conditions necessary for a definite diagnosis are the positive agglutination reactions of the dysentery bacillus with the blood serum of the patient, and the isolation of the bacillus from the dejecta of the patient or from the organs of the dead.

Attention must be paid to exclude carcinoma, polypi, and syphilis of the rectum, hemorrhoids, and mercury poisoning. Amœbic dysentery must be differentiated etiologically, clinically, and anatomically, from bacillary dysentery. The following are the most important points in this: 1. Amœbic dysentery usually runs a chronic course. 2. In the amœbic form no dysentery bacilli can be found, except in the mixed infections of both amœbic and bacillary dysentery. 3. In amœbic dysentery toxic symptoms, such as high fever, general malaise, anorexia, rapid emaciation, or various nervous symptoms are not observed. 4. In bacillary dysentery liver abscess is never present; it is a very frequent complication of amœbic dysentery. 5. The anatomical processes are also different. According to Kartulis and Kruse, the edges of the ulcers are peculiarly undermined in amœbic dysentery, while in bacillary dysentery this is never the case and the ulcers are situated on the surface of the folds of the mucous membrane.

Bacteriological Diagnosis.—In this the agglutination of dysentery bacilli with the blood serum of the patient, and the isolation of the bacillus from the dejecta, are required, with the following methods:

1. In general, a positive *agglutination* reaction is first present in dysentery during the second or third week of the disease, and during convalescence reaches its highest point, then gradually subsiding in intensity. Occasionally it appears for the first time at the end of the sixth week. This reaction, however, is of little value in the diagnosis, as often it is first present too late and it is not constant. The reaction is usually also weaker than in typhoid fever. When the reaction occurs in a dilution of 1 to 20, it must be regarded as positive. Usually the reaction occurs in 1 to 20 to 50 dilution. Occasionally in mild dysentery the reaction is negative (1 to 10). According to Kruse, the reaction in dysentery is higher and in one case was positive at 1 to 1000 dilution. It seems to me that the reaction is usually higher in the infections caused by the mannite fermenting bacilli than in those caused by the bacillus of type I.[1]

The problem of the reaction is not simple, because there are many types of dysentery bacilli, each of which can be highly agglutinated only by its own blood serum, even among the mannite fermenting types. The reaction can be also more or less used in estimating the prognosis of dysentery. According to my own observation, two prognostic facts may be deduced: (1) If the agglutination reaction quickly increases in intensity the prognosis is favorable. (2) The prognosis is unfavorable or doubtful (unless the disease is very chronic) if the intensity of the agglutination reaction does not increase, or, if at all, but slightly.

2. *Isolation of dysentery bacilli* from the stools is only of limited application, because it is rarely successful in mild cases and during the first days of the disease. If, however, the localization of the process is in the lower portion of the large intestine, the *B. dysenteriæ* is present early in the stools and the bacilli are especially numerous in slimy dejecta mixed with fresh blood. For the isolation of dysentery bacilli from the stools it is best to take up first some slimy flecks, and after a short washing in sterilized water put the material directly into the culture medium. (1) Superficial smearing upon the agar plate with a right-angled bent glass rod (v. Drigalski) or the glass stopper of a glass bottle (Ohno), both sterilized. (2) The superficial smearing upon v. Drigalski's litmus-lactose-agar[2] or Endo's fuchsin agar.[3]

The colonies of dysentery bacilli on the agar plates are smaller, lighter in color, and more transparent than those of colon bacilli. The colonies on the Drigalski's plate can be examined in sixteen hours. The colon bacillus and the group of saprophytes make the medium acid by the decomposing of lactose, and the colonies become red in color in its neighborhood, while the dysentery bacillus causes no change in color because of not decomposing lactose. The colony of the latter is round, with sharp contours, almost as clearly transparent as dew-drops and about 1 mm. in diameter. On Endo's medium the dysentery bacillus makes a colorless

[1] In some cases caused by the bacilli of type IV, Ohno found a high agglutination above 1 to 3000. Duval reported also some similar cases caused by the so-called Duval bacillus.

[2] V. Drigalski and Conradi, *Zeitschr. f. Hyg. u. Inject. Kr.*, 1902, Band xxxix; Lentz, "Dysenterie," *Kolle und Wassermann's Handbuch der path., Microörg.*

[3] *Centr. f. Bact.*, 1903, Band xxxv, No. 1.

or only light red thin colony while that of the colon bacillus seems thick and deepred. The further examination of the colonies proceeds with the agglutination phenomenon done by the hanging-drop examination of slight dilutions of dysentery serum (most conveniently done with rabbit serum of high agglutination power). When this proves positive, the glucose agar culture and cultivation in milk are done. If no gas is produced and the milk is not coagulated, while the bacillus has no mobility, then the microörganism may be regarded as *B. dysenteriæ*. To know the type of bacillus it is necessary to test the fermentation upon carbohydrates and the agglutination with specific sera of every type.

Prognosis.—The localization of the lesions in the intestines must be known, for if they are limited to the sigmoid flexure or rectum the prognosis is favorable, but if the transverse and ascending colon or the small intestine is involved the prognosis must be given very cautiously. The higher the lesions in the intestine the more marked are the intoxication symptoms and the more unfavorable the prognosis. Nervous symptoms and other toxic manifestations set in when the upper portion of the large intestine or the small intestine becomes involved. They are very unfavorable, and patients showing them usually die.

As regards sex, the mortality among females is larger than among males. In infants under the age of five years and adults above fifty years the prognosis is unfavorable. The mortality of epidemic dysentery is small in the beginning of the epidemic (May, June, and July), and increases gradually, reaching the maximum at the end of the epidemic (in November and December). In winter we have a higher mortailty caused by the influence of the season and the chronic course.

Treatment.—This involves: (1) Keeping the patients absolutely at rest and having them warmly covered; (2) inhibiting the factor in the intestine; (3) attending carefully to the diet; and (4) proceeding with the etiological treatment.

The diagnosis being established, the patient should at once be sent to bed, which has a marked influence. Repose must be as nearly complete as possible. It is necessary to cover the patient warmly, and a woollen abdominal bandage is advisable.

The indication of rest we meet further by stopping all solid food. The diet should be taken in small quantities at a time—a little every two or three hours. The tongue is a fair index to the food most likely to suit the patient. When this is coated, small quantities of thin chicken broth, egg albumen, thin barley or rice-water are taken better than milk; when the tongue is or has become clean, then milk—pure, diluted with barley or rice-water, or peptonized—is the best diet. In Japan we are accustomed to give rice gruel, eggs, and fish (the so-called "sashimi"). Alcohol is not recommended, but in case of collapse a small quantity may be given with advantage. The food must be given neither hot nor cold, as food when either too hot or too cold is apt to excite peristalsis and cause colic and straining.

Most authors are agreed that calomel has the best effect in the beginning of the disease. The writer uses it to clear out the bowels and remove the infectious material, in order to hinder the extension of the

disease upward, 0.5 to 0.8 gm. (8 to 12 gr.) of calomel may be given once or twice, or 10 to 20 cc. (℥iij to v) of castor oil, which is to be given but once. In other cases one can give 0.5 gm. calomel, and after an interval of one or two hours, 10 to 15 cc. of castor oil. Plehn recommends giving the castor oil (15 cc. [℥ss]) first, and beginning the next morning, hourly for twelve hours, a tablet containing 0.03 gm. (gr. ½) of calomel and 0.3 gm. (gr. vj) of calomel in all. The same is done during the next two days being omitted in the night.

The patient is ordered simple acid lemonade or tartaric acid lemonade or alkaline waters. Enemata of 1 per cent. saline or soda solution are also recommended to remove the infectious contents of the bowel and to assist regeneration in the mucous membrane. By the use of enemata tenesmus is diminished and there is less disturbance. Enemata of silver nitrate, tannin, or quinine solutions and the like are not recommended in acute dysentery. Berther used enemata of methylene-blue solution both in tropical and bacillary, dysentery with good results. According to him, the effect of methylene blue is based upon the following points: (1) Its bactericidal action is not absolute, but it diminishes the virulence exceedingly. (2) It decreases reflex action by its analgesic effect, and excites the secretion of bile remarkably, which acts as a disinfectant and the secretion of which is very much diminished in dysentery. (3) Vomiting is also influenced favorably by giving the remedy internally. This remedy may be given as irrigations (½ to 1 liter with 0.1 to 0.2 gm. of methylene blue). These are conveniently given after a stool with the patient in the knee-chest position. Internally we give doses of 0.1 to 0.2 gm.

For the tenesmus, suppositories of cocaine, opium, or extract of belladonna may be used. For the hemorrhage from the bowels, an ice-bag is applied over the abdomen, and opium is given internally. The patient must be absolutely at rest. Injections of ice-water or of 0.1 per cent. ferric chloride solution are recommended. For collapse the subcutaneous injection of physiological saline solution is effective.

Other so-called dysentery remedies, which are well known and used generally, such as ipecacuanha, pomegranate bark, antidysenteric pills, and others, are entirely ineffective; certainly they are superfluous remedies in the treatment of bacillary dysentery. Ipecacuanha is of little value in bacillary dysentery. The astringents are also unsuitable in the stage of inflammation.

Treatment of Chronic Dysentery.—The chronic form is to be considered rather as a sequel, because in this stage the dysentery bacillus has disappeared from the stools and only mucus or pus is passed. This form is very obstinate and recovery is difficult. We can try enemata, as silver nitrate (in dilution of 1 to 500 to 1000), tannin (0.25 to 0.5 per cent. solution), thymol (1 to 500 to 1000 dilution), resorcin (1 to 2 per cent.), creolin (1 to 2 per cent.), lysol (1 per cent.), and the like. In some cases the author has tried enemata with gum Arabic mixed with bismuth, subgallate of bismuth, or iodoform, with better results (mucilage of acacia and water āā 50 cc., bismuth subnitrate or subgallate 5 gm., or iodoform 0.5 gm.). As an internal remedy we often order salol, tannigen, etc.

Serum Treatment.—*Immunization of Horses against the Dysentery Bacillus.*—An agar culture of the dysentery bacillus which has been maintained at incubator temperature for twenty-four hours is emulsified in normal saline solution and heated at 60° C. for half an hour. Gay prefers instead of heat the use of a 0.5 per cent. mixture of tricresol with glycerin. The mixture is then inoculated subcutaneously into horses in the usual manner, beginning with small doses, which are gradually increased in amount. For immunization the bacillus must be virulent, and the bacillus isolated directly from the patient is more virulent and effective than the bacillus obtained after passage through animals. The author therefore always preserves the direct stick agar culture of the first generation isolated from the stools for immunization.

Practical Serum Treatment.—The dysentery serum is bactericidal as well as antitoxic (Todd, Rosenthal, Kraus). In dysentery the lesions are usually localized in the rectum and lower portion of the large intestine, the pathological function of which is principally mechanical. The toxic symptoms are intimately connected with this localization, against which bactericidal serum is valueless. Such symptoms in dysentery are happily less prominent than in typhoid fever. This conception also accounts for the very unfavorable prognosis in enterodysentery. It is already reported that there is a fitted complement in the human body for the dysentery serum. This is advantageous for the use of a dysentery serum of bactericidal nature.

In accordance with my researches, I have formulated the following rules for the administration of dysenteric serum in the Institute for the Research of Infectious Diseases in Tokio: (1) In mild cases the serum is injected once in a dose of 10 cc. (2) In cases of medium severity the serum is twice injected in doses of 10 cc. The interval is from six to ten hours. (3) In severe cases the largest amounts of serum are injected (about 40 to 60 cc.), but the daily dose does not exceed 20 cc.

By serum treatment the disease in its first stages is quickly cured or markedly ameliorated. In one or two days after the injection, the process is affected, the blood and mucus disappear, pain and tenesmus cease, and the patient seems entirely well. On the later use of the serum (at the end of the first week) improvement of all symptoms occurs on the next day after the injection. The number of stools is markedly diminished and the tormina and tenesmus decrease. After a few days, remarkable improvement is to be seen. The blood in the stools diminishes or entirely vanishes, the appetite increases, and the general condition is much improved. The recovery happens usually after a week. The effect of the serum upon the fever is very striking; the fever may be lowered even below normal on the next morning after injection in the majority of cases. In the ulcerative stage the action of the serum is not so pronounced as in the earlier stages; nevertheless healing of the ulcers with cicatrization often takes place. In such cases, however, the fever is reduced, the number of stools is markedly diminished, the general condition is improved, and the appetite increases. Even in this stage the results are far better than those by any other method of treatment.

The mortality under the use of the serum was reduced to one-third,

at least less than one-half from that obtained by medical treatment (from 22 to 26 per cent. to 9 to 12 per cent.). In Russia, Rosenthal has only had 8 deaths among 157 cases (5.1 per cent. mortality) under serum treatment, while the mortality in Moscow is between 12 and 17.5 per cent. without serum treatment.

Polyvalent Dysenteric Serum.—A polyvalent serum powerful against all types of dysenteric bacilli is highly recommended. The author succeeded in preparing a serum of this kind by alternate immunization of horses with the three types of dysenteric bacilli. Since 1906 he has attained much better results through the use of this serum.

Prophylaxis.—Prophylaxis must be based upon the knowledge of the methods of infection. Here we describe only the protective inoculation. The author performed active immunization upon himself in 1898. But the method is not applicable generally, because the inoculation of the dead bacilli causes serious inflammation and also general disturbance. The author came finally to the so-called simultaneous method, in which both the dead bacillus emulsion (heated at 60° C. for thirty minutes) and specific immune serum are simultaneously injected. The animal experiments showed that in fact after one injection of the material, active immunity was procured, guinea-pigs being thus protected against three times the lethal doses for at least three weeks. The simultaneous immunization upon human individuals is also accompanied by only a slight reaction, and is performed as follows: taking the whole quantity of the bacilli from an agar slant culture after twenty-four hours, mixed with 10 cc. sterile normal saline solution and heated at 60° C. for half an hour, we mix it with the same quantity (10 cc.) of immune serum. The mixture thus obtained is used for the first injection. Five days later the second mixture, containing the bacillus emulsion and serum in the ratio of 4 to 1, is injected. The doses for certain ages are as follows: six to fifteen years, 0.4 to 0.8 cc.; sixteen to fifty years, 0.8 to 1 cc.; and fifty years and over, 0.6 to 0.8 cc.

In the blood serum of individuals thus treated the presence of the protective body was proved after twenty days, and even after thirty days in the animal experiment. In the years 1898–1900 the author tried preventive inoculation on about 10,000 men in the district of Japan where epidemic dysentery prevails most seriously, and diminished the mortality in the district from 20 to 30 per cent. to about zero.

By protective inoculation the mortality has decreased, but not been entirely abolished. Considering the fact that local immunity has a better result, the author made experiments in applying the heated emulsion to rabbits per os to protect them from the disease. These experiments showed that this direct immunity of the mucous membrane of the bowels is the best for the purpose. The only disadvantage of preventive inoculation is that we can obtain the immunity only after an interval of eight days after inoculation, while the duration of the immunity is only about two months. Therefore the author recommends the injection of immune serum in small quantity (5 to 8 cc.), if we require to get the protective power quickly in case of family epidemics.

PART II

DISEASES OF DOUBTFUL OR UNKNOWN ETIOLOGY

CHAPTER XXII

SMALLPOX

By WILLIAM T. COUNCILMAN, M.D.

REVISED BY

E. J. G. BEARDSLEY, M.D.

Smallpox (Latin, Variola; French, La petite Verole or La Variole; German, Blattern or Pocken; Italian, Vajuola; Spanish, Viruelas) is an acute infectious disease characterized by a sudden onset, usually with a chill or chilly sensations, a febrile stage of three or four days' duration, in which the patient usually complains of dizziness, headache, backache, general body pains, nausea, gastric distress, and vomiting. On the third day of the disease a general minute macular eruption appears which, in the succeeding eight days, passes through the stage of papule, vesicle, pustule, and crust. After recovery the seat of the cutaneous lesion is marked by scars whose extent and depth depend upon the character of the original pustules.

Variola is the most characteristic of the acute exanthemata, and in no other disease in man do the various stages succeed one another with such regularity. This is apparent in the literature, for the clinical descriptions of the disease from Sydenham to the present time present great uniformity, and there has been but little added to the description given by him over two hundred and fifty years ago. Smallpox is highly infectious, and no immunity is given by race, sex, age, or season. Notwithstanding this, so great is the protection given by vaccination and revaccination that a large majority of physicians have never seen a case of smallpox, and in civilized lands we rarely see an individual bearing the cicatrices produced by the disease.

The disease is infrequently seen, but its presence is continued by the ignorant or by the careless. The floating population who do not acquire a residence so as to be subject to vaccination laws are often responsible for epidemics. The disease is also kept in existence by a class of people with that peculiar order of mind which renders them incapable of sane judgment, and who seek in every way to oppose vaccination and

revaccination not only for themselves but for others. One of the saddest features is that in every epidemic there are a number of unvaccinated children in no way responsible, who either die of the disease or are permanently disfigured or blinded.

Incidence.—No acute infectious disease shows such a complete independence of the conditions of race, climate, and soil as does smallpox. It thrives equally well wherever its contagion may be carried and where

Fig. 19

The dark lines represent the number of cases of smallpox in Massachusetts for each month in 1901, 1902, and 1903. The dotted lines represent the deaths. Notice the great decline in mortality at the end of the epidemic. $2\frac{1}{2}$ mm. equal 10 cases.

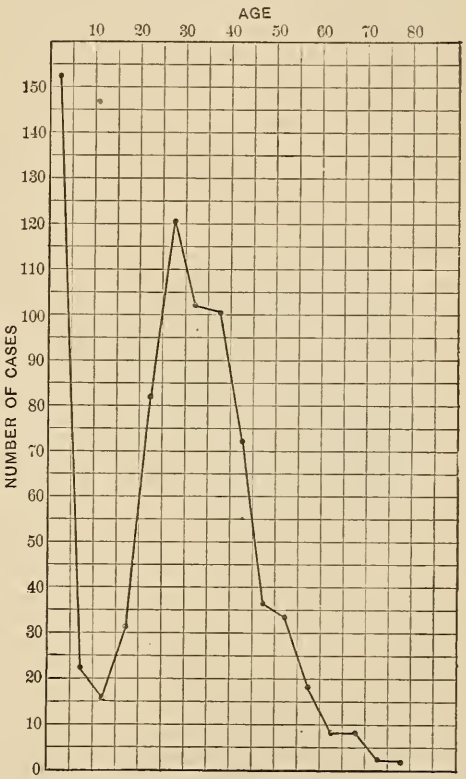
it finds a susceptible population. The susceptibility of the population varies. During and after each appearance of smallpox in a community, vaccination is carried out vigorously and the susceptibility is diminished or rendered *nil* by vaccination or by an attack of the disease. With the passing of the disease, vigilance relaxes and the number of susceptible individuals increases. The disease is kept in existence by sporadic cases, which furnish the virus, and with this and susceptible material there

will be an outbreak. There is an irregular periodicity in the outbreaks of the disease also shown in epidemics of the prevaccination period.

The season of the year has an influence on the morbidity and upon the diffusion of the epidemic. Rhazes says that in Arabia epidemics occurred at all seasons, but generally began at the end of the autumn, or in the early spring, or in the cold season. Even here there is much irregularity; in England, for instance, between 1837 and 1840 there were 9095 deaths in the winter, 9470 in the spring, 10,005 in the summer, and 12,483 in the autumn. The epidemics in America of 1882 and 1902 reached their height in the winter and early spring. Fig. 19 shows the influence of season on the disease in the outbreak in Massachusetts, from 1901 to 1903.

The mortality seems to be greater during the height of the epidemic than at its decline, as is shown by the chart. The mortality varies greatly in different epidemics, this being true both of the prevaccination era and now. From 1901 to 1903 there were epidemics in various parts of the United States in which the mortality was as low as 2 per cent. The mortality in the epidemic in Philadelphia at that period was 26.89 per cent. in 7204 cases. In Massachusetts in the years mentioned the mortality was 11 per cent. It is not certain that children are naturally more susceptible to the disease than adults. The cases among them decrease in frequency after the tenth year, owing to compulsory vaccination when they enter schools. This is shown in the table of ages (Fig. 20) of 800 consecutive cases in Boston. The mortality in patients aged under one year is always high because no vaccinated cases are found, and without the modification produced by vaccination smallpox in infancy is practically always confluent unless the epidemic is a particularly mild one.

Fig. 20



Curve of ages of 800 cases of smallpox. Notice the extraordinary decline at 8 years. (School vaccination.)

Race seems to exert little influence either on morbidity or mortality. When the disease is introduced into aboriginal tribes the mortality is extremely high. The first outbreak of smallpox in the Western hemisphere occurred in the West Indies in 1507, and entire tribes were

exterminated. The disease reached Mexico in 1520, imported by troops from Spain, and the number of deaths in a short period of time has been estimated at 3,500,000 In the epidemics in this country, cases are always relatively more numerous among the negroes, and the mortality among them is higher. Both the increased morbidity and mortality are due to the greater percentage of unvaccinated persons. Welch and Schamberg found a mortality of 49.45 per cent. in unvaccinated negroes, and 44.69 per cent. among the whites.

Etiology.—No bacterium peculiar to the disease has been found; in many cases it is not possible to demonstrate bacteria either microscopically or culturally in the specific lesions; when bacteria are found they are present in the advanced lesions rather than in the young and developing lesions. Lesions peculiar to the disease have not been produced by inoculating animals with pure cultures of the bacteria found.

The included bodies in the epithelial cells of the lesions, which have played an important role in the later attempts to discover the etiology, were first described by Weigert in 1874. Guanieri, in 1892, gave the first clear description of the bodies which he regarded as parasitic protozoa and the cause of both vaccinia and smallpox. He described bodies in the deep-lying epithelial cells of the skin in vaccinia and smallpox pustules, as well as in the epithelial cells of the cornea of rabbits which were inoculated with either vaccine or variola virus. He found the bodies lying in clear spaces adjoining the nuclei of the epithelial cells, and varying in size from that of a micrococcus to that of the nucleus of a cell. He gave the organism the name of "*Cytoryctes variolæ*," the name having reference to the supposed property of the organism of devouring the epithelial cells and in this way forming a space within which the organism lies.

Since the publication of Guanieri, a number of articles with reference to these bodies have appeared, which have been, in the main, confirmatory of his description and interpretation, but which with few exceptions have added little to our knowledge of their more intimate structure or nature. Up to 1904 the most important article confirmatory of the views of Guanieri was that of Wasielewski in 1901. He also regarded the bodies as parasites and the cause of the disease. The organism enters the epithelial cells, and its first influence is to produce an increased nutrition and enlargement of the cell. He showed, further, that no other injury to the cornea of the rabbit and no other form of infection produced lesions of the same character as those produced by inoculating the cornea with vaccine or variola virus. In the lesions he always found these bodies and no other foreign structure. He showed that the virus increased in the lesions, for he could inoculate from eye to eye indefinitely without any change in the character of the lesions. He inoculated from the cornea of the rabbit to the calf in the fifteenth and twenty-fifth generations, and in each obtained perfectly typical vaccine pustules and immunity to further vaccination. Children were vaccinated from the cornea of a rabbit in the thirty-sixth generation, and typical vaccinia resulted.

There have also appeared a number of articles which oppose the

views held as to the parasitic nature of these bodies. By some they are regarded as the products of degenerations in the epithelial cells; by others as leukocytes which have become included in the cells; and by still others as red blood corpuscles. In the studies which were carried out on smallpox and vaccinia in 1902 and 1903 by Councilman and his co-workers, these bodies were unqualifiedly regarded as parasites and the cause of the disease. In the course of the work important additions to our knowledge of the structure of these bodies, their cycle of development, and their etiological significance were made.

In the skin lesions of smallpox, and particularly in the earlier stages, certain small bodies are seen in the epithelial cells. These bodies show a variation in size, external form, and internal structure. The smallest are less than 1 μ in diameter. They lie usually in a vacuole of the cell close to the nucleus, and usually but a single body is found in a cell. Occasionally two are found lying on opposite sides of the nucleus, and in rare instances they have been found between the epithelial cells. The appearance of these bodies is coincident with the earliest changes in the epithelial cells. They may be found in cells which show no other change, and in cells whose nucleus is dividing. When first seen, these bodies are refractive and homogeneous in the unstained specimens, and stain slightly with most staining reagents. From such forms there is a progressive development. They enlarge and preserve their homogeneous character, remaining round or oblong until they reach the size of 4 to 6 μ. At this stage clear spaces appear in them, and in the middle of the clear space a small dot, which in specimens stained with methylene blue and eosin usually stains blue, while the remainder of the body assumes a reddish tint (Fig. 21). With the increase in size of the body, the degeneration of the cell enclosing it progresses and the enclosing space enlarges. The body increases in size until it becomes as large or larger than the nuclei of the epithelial cells. It no longer preserves its round or oval sharp outline, but becomes elongated, irregular, and sometimes assumes an hour-glass form. The structure increases in complexity, and shows, finally, small round bodies enclosed in a reticulum. The reticular structure breaks up and the enclosed small bodies lie free in the vacuole of the cell. The vesicle of smallpox develops from a single point in the skin, and from this there is extension in all directions to a variable extent. In early vesicles it is possible to recognize a central older area and a peripheral area of extension. In the oldest area the most developed of the cytoplasmic inclusions are found, and in the periphery the smallest and presumably youngest forms. The conclusion is inevitable that the progressive development of the

FIG. 21

Two of the larger cytoplasmic forms of cytoryctes in the epithelium. The two dark bodies in the middle showing reticular structure are the parasites. × 1000.

vesicle is due to an increase of the virus and its dissemination in the surrounding epithelial cells.

Inclusions in the cytoplasm of the cells only are found in the earliest lesions. In the late vesicular stage and in the beginning pustule, new structures begin to appear in the nuclei of the epithelial cells in the centre and oldest portion of the lesion in which the cytoplasmic inclusions have disappeared. The nuclear inclusions begin with the appearance of one or several small circular masses in the nucleus. These have a sharp outer rim and a clear homogeneous refractive content. They increase in size, and with growth show a greater complexity of structure. The form varies; at times the entire structure appears to be composed of an infinite number of small circles, in the centre or at the side of which small stainable points can be made out. In other cases there is a large central space around which are grouped a great number of very small spaces all bearing the central dots. (Plate XVIII). The nucleus enclosing these bodies enlarges, the central chromatin disappears, leaving only a thin, faint, nuclear rim, which finally disappears, the enclosed bodies are set free, and they may be found in the central mass of broken-down cells, mixed with exudation. In the degenerated nuclei there are often found small, refractive, brightly staining points measuring less than 0.5μ in diameter.

In all vaccine lesions, whether in man, in monkeys of various species, or in the calf or rabbit, bodies essentially similar to those included in the epithelial cells in smallpox in man, and undergoing the same changes and development, are found. There is no difference in the size, relative numbers, and course of development, of these bodies, whether the tissue chosen for the site of vaccination be skin, mucous membrane, or cornea. All competent observers agree in this. If the rabbit or calf be similarly inoculated with material from smallpox lesions in man, a lesion is produced which is essentially the same as that produced by vaccination, and the same inclusions are found in the epithelial cells. The results of the two processes are in all respects the same, and immunity from both smallpox and vaccinia is conferred. It is known that many of the strains of vaccine lymph have been derived from the calf inoculation with smallpox virus. Neither the calf nor any other of the domestic animals is susceptible to smallpox. The disease which they acquire by inoculation with smallpox virus is vaccinia.

Neither in man nor in the monkey, nor in any other animal experimented with, are the nuclear bodies found, when vaccine material is used for inoculation. Typical vaccine lesions without general eruption are produced and only the cytoplasmic inclusions are found in the lesions. The same is true of the rabbit and calf when smallpox material is used for inoculation. When smallpox material is inoculated in the monkey, after an incubation period of about eight days there develops an exanthem, varying in extent, and differing in nowise, save in being less extensive, from the exanthem of smallpox. In the lesions of this, the nuclear inclusions in the same form and undergoing the same development are found along with cytoplasmic forms. Inoculation of the smallpox exanthem from monkey to monkey results in smallpox with

PLATE XVIII

FIG. 1

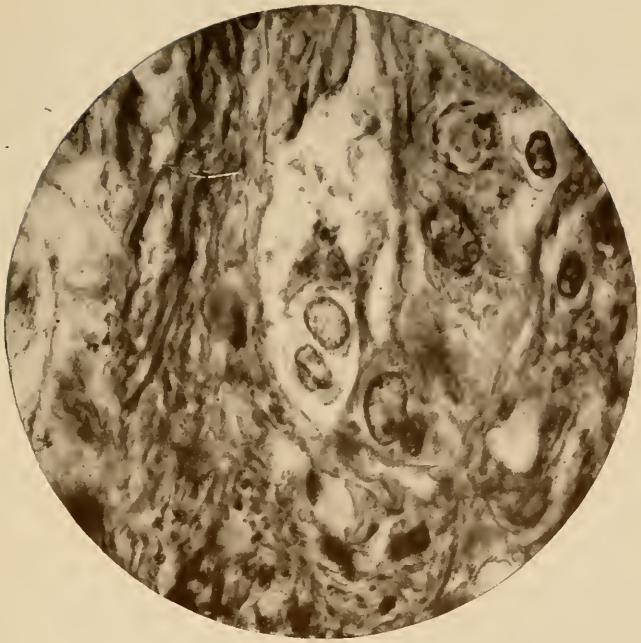
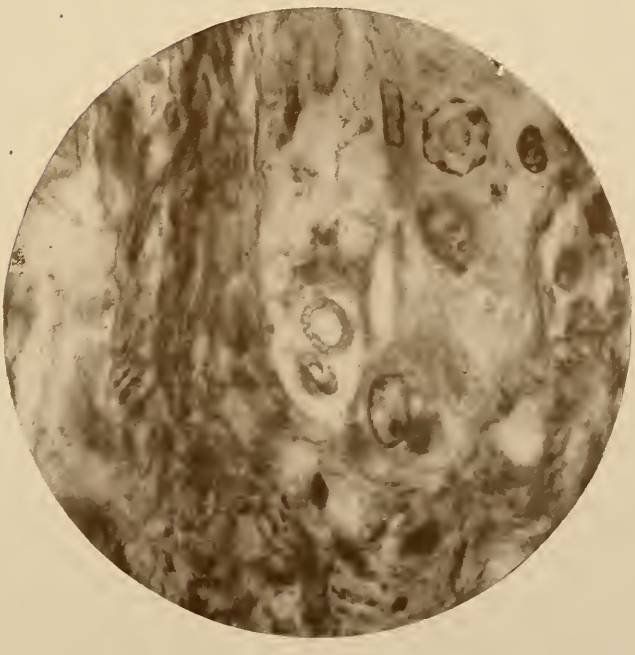


FIG. 2



Free-lying Intranuclear Parasite, with Adjoining Nuclear Fragments.

In Fig. 1 the surface view is given; in Fig. 2 the optical section through the centre.

exanthem and with nuclear bodies. Inoculation from the monkey with smallpox to the rabbit results in vaccinia without the nuclear inclusions. These bodies within the nuclei are characteristic of smallpox. It has seemed that the organism in smallpox and in vaccinia was the same, that in vaccinia it only reached a degree of development comparable in a general way to the asexual self-infecting cycle of the malarial organism; that in smallpox, in addition to this development, which takes place in the cytoplasm of the epithelial cells, there is a further development, comparable to the sexual cycle of the malarial organism, which takes place within the nucleus.

The small spore-like bodies found in the skin lesions in the later stages probably represent the final spores which are the true agents of infection in smallpox. There is one very striking difference in the manner in which infection takes place in vaccinia as compared with smallpox, and which is only to be accounted for by differences in the character of the infecting agent. Infection takes place in vaccinia only when the virus is placed in contact with suitable epithelial cells of the skin or mucous membranes. Infection rarely takes place in any other way than by design, though there are cases of accidental infection. Infection in vaccinia does not take place by air transmission and does not follow from patient to patient. In smallpox infection usually takes place by air-borne infectious material.

Pathological Anatomy.—The Mucous Membranes.—Eppinger was the first to call attention to the frequency and gravity of the lesions in the mucous membranes; their presence was known to the early investigators. The specific lesions in the mucous membranes show a general resemblance to those of the skin, although there are modifications due to the differences in the tissues. The epithelial cells are in much looser connection with each other, the tissue is more easily permeated by the exudation, and the horny layer is absent. The specific character of the lesion is apparent only in a very early stage. The epithelial cells which are first affected, together with the cells adjacent to them, are thrown off by the exudate, leaving an area bare of epithelium. This takes place more quickly on surfaces covered with cylindrical than on those covered with squamous epithelium. The lesions develop in the same way as in the skin—by the infection and degeneration of circumscribed foci of epithelial cells followed by exudation. The hyaline fibrinoid degeneration takes place as in the skin. In addition to the specific lesions in which the parasites of the disease are found, there are more serious lesions which are non-specific, and at autopsy most frequently found in the soft palate and uvula. They consist chiefly in superficial loss of substance with deep necrosis of the underlying tissue. In these places masses of streptococci are found. Numbers of polynuclear leukocytes are found in these lesions in contrast to the specific lesions. Vesicles produced by the uplifting of the entire epithelium are rarely found in the mucous membrane. The specific eruption may be found in the mucous membrane of the mouth and fauces, in the larynx, rarely in the trachea and bronchi, and in the œsophagus not infrequently. Only in 1 out of 54 examinations was a specific lesion with the parasitic inclusions found in the

mucous membrane of the stomach. In 2 cases a pustule was found in the penile portion of the urethra. None were found in the vagina nor in the female urethra.

Lungs.—The most common lesion is bronchitis, usually combined with more or less extensive bronchopneumonia. Both the large and small bronchi are affected. In 54 autopsies such lung lesions were found in 43. Lobar pneumonia was found in 2 cases. In 8 of the cases the lung exudate was largely hemorrhagic in character, and in 4 cases of purpuric smallpox, hemorrhages were found both in the lungs and on the pleura without any evidence of pneumonia. Different varieties of pyogenic cocci are constantly found in the foci of bronchitis and bronchopneumonia. The streptococcus is most commonly found and next the pneumococcus. The lung lesions are found in all stages of the disease from the earliest to the latest. They are the most common and most serious complications of smallpox. In many cases they are so extensive as to form a sufficient cause for death without the specific disease.

Liver.—The liver is generally enlarged. The largest livers are found in the late pustular and crusting stages. The only condition to which this increased weight can be ascribed is the very evident swelling of the cells, which are larger and more granular than normal. We are accustomed to regard the liver in typhoid as the type of cloudy swelling, but the increase of weight in typhoid (average 1893 grams in 64 cases) is slight as compared with the increase in smallpox. The fat of the liver is not increased. In 6 of the 54 cases necroses were found. In 3 this took the form of the ordinary central necrosis of the lobule, and in only 1 case was it extensive. In 3 cases there were not distinct foci of necrosis, but single necrotic cells were found without any relation to the lobule.

Spleen.—This is commonly enlarged in the late pustular stages. The spleen differs in smallpox from that of the other acute infectious diseases in the great diminution in number or the absence of polynuclear leukocytes. In the hemorrhagic forms, and in the early period of the ordinary types up to the completion of the pustular stage, it contains in some cases no recognizable polynuclear leukocytes. In the period of desquamation polynuclear leukocytes are fairly abundant.

Glands.—The lymph nodes are swollen in the beginning of the disease; the swelling persists or increases during the period of eruption, and slowly diminishes. The most common condition is a general œdema producing dilatation of the sinuses and separation of the cells of the follicles. The enlargement of the nodes is due more to this œdema than to cellular hyperplasia. Numbers of large basophilic cells are found both in the sinuses and in the follicles. Phagocytic cells are always present; they are most numerous in the later stages of the disease, and are confined chiefly to the sinuses. They are formed by the proliferation of the endothelial cells. Streptococci are frequently found in the sinuses.

Bone-marrow.—Chiari, in 1893, investigated the marrow in 22 cases embracing all stages of the disease, and found changes in 86 per cent. He described under the name osteomyelitis variolosa, foci of necrosis and hemorrhage associated with the presence of large cells. The more

recent studies of the marrow have been in connection with the changes found in the blood. The polynuclear cells were almost entirely absent, and the neutrophile myelocytes diminished in number, with only a few of them in mitosis, and occasionally degenerated.

In the examination of the marrow, the writer has found, like others, marked reduction and in some cases complete absence of the polynuclear leukocytes. In one case which died during convalescence, the marrow corresponded to that of active leukocytosis. The absence of leukocytes does not seem to be due to their degeneration and destruction *in loco*, for, save in the purpuric cases, degeneration forms and nuclear detritus are not found. Foci of necrosis varying in size from those easily visible to microscopic areas are found as Chiari described. In early cases there is no reaction around the necrotic foci. In cases dying in advanced and crusting stages, collections of large cells are found in the fat-spaces around the necrosis. Definite myelocytes are not numerous, and the forms of these with incurved nucleus, the immediate predecessors to the polynuclear cells, are also rare. The most numerous cells in the marrow are basophilic cells, similar to those described in the spleen and lymph nodes. Nuclear figures are numerous in these cells, many of which approach very closely to the character of plasma cells. Cells of a typical lymphoid character are found in varying numbers, and are more abundant in children than in adults.

Eosinophilic cells are less numerous than in the hyperplastic marrow of other infections. Those found correspond chiefly to the eosinophile myelocyte; those with nuclei of the polynuclear type are as generally absent as are the polynuclear neutrophiles.

The large cells first described by Chiari are found in relation to the necrotic foci, and independently of these. They occur both singly and in groups, often surrounding the fat cells. They are phagocytic for all of the cells of the marrow. They are most numerous in the cases in which there is most hyperplasia in the marrow. Comparison of the marrow of smallpox with that of other infectious diseases has led the writer to regard these groups of large cells as occurring in smallpox alone. They are found in other infections, but not in the same number and grouping. Their chief function seems to be fat absorption. Cells with the same relation to the fat cells are found in fat necrosis and in inflammation of the mesentery and omentum.

In cases of purpuric smallpox, hemorrhages of considerable extent may be found in the marrow. Osteomyelitis variolosa is a bad term to apply to the small necrotic foci, as it magnifies their importance. We understand by osteomyelitis an entirely different pathological condition, and one which the writer has never found as a complication of smallpox.

Testicle.—The lesions most difficult of interpretation are those of the testicle. There is absence of spermatogenesis save in the cases in which convalescence is established. Normal spermatozoa are absent in the lumina of the tubules, and there is degeneration of the spermatogenic cells. This affects both cytoplasm and nuclei, and the degenerating nucleus assumes forms which present some similarity to certain of the

intranuclear parasites in the epithelial cells of the skin. This degeneration is not peculiar to smallpox, but may be found in typhoid fever. These lesions are absent in undeveloped testicles of children.

In addition to these diffuse degenerative lesions, there are focal lesions as characteristic of the disease as the skin lesions, which are found both in the undeveloped testicles of children and in the adult. The lesions begin as an infiltration of the intertubular tissue with both ordinary lymphoid cells and large mononuclear basophilic cells. The tubules in the foci are unaltered. From such lesions as these, which are best compared with small interstitial foci in the kidneys, the process extends. The area enlarges, the cellular infiltration extends, and finally there is complete necrosis in the centre, with fibrin and hemorrhage in the surrounding interstitial tissue. The necrotic tubules often contain numbers of phagocytic cells. The bloodvessels in the foci are obliterated in some cases by thrombi, but chiefly by the pressure of the cells. Acute endarteritis with accumulations of mononuclear cells is often found.

The lesions vary in number, some testicles showing large numbers of them, while in others they are found only after prolonged search. The smallest lesions, and those best adapted for study, are in the undeveloped testes of children. They show a general relation to the duration of the disease, the most advanced cases occurring late in the course. In 3 of our cases, lesions similar to those in the testicle were found in the epididymis, and in 1 case in the prostate. Brinckerhoff and Tyzzer have found lesions in the seminal vesicle of the monkey in variola inoculata. Cytoryctes were present in the epithelium involved in these lesions. Notwithstanding their apparently specific nature, no parasites were found in the testicular lesions of man.

Kidney.—Unrah, in 1872, first called attention to hemorrhage in the pelvis, finding it in 28 of 212 cases. The writer found it in 5 of 54 cases. The epithelial surface is intact, the hemorrhage taking place in and beneath the mucous membrane. It is found in cases in which there are hemorrhages in other organs. It has no connection with hemorrhagic nephritis, this being a rare complication of the disease. The hemorrhage is confined to the mucous membrane of the pelvis and does not extend into the ureters and bladder. In cases of hematuria this pelvic hemorrhage seems the most probable source of the blood.

The kidneys are affected in all cases; the most common change is acute degeneration of the epithelium, which occurs in all stages of the disease and at all ages. The kidneys are usually enlarged, rather œdematous, and opaque on section. In 5 cases out of 54, acute glomerulonephritis was found, and in one it developed during convalescence.

Heart.—Cardiac lesions are infrequent. The writer found acute vegetative endocarditis in 1, an adult who died on the ninth day. There is usually no enlargement of the heart save in patients in whom there is nephritis. Fat is not infrequently found in the muscle fibers. In 3 cases, 2 of them purpuric smallpox, small but well-marked foci of degeneration were found in the muscle close beneath the endocardium.

Inoculation Smallpox.—There is one form formerly of great importance, but which recently has received scant attention and its leading

characteristics have been overlooked. This is the inoculated smallpox (variola inoculata) produced by the direct inoculation of the vesicle or pustule contents from man to man. The disease so produced differed in marked degree from true smallpox. These differences were always the same and were not due to accidental causes. The period of incubation was eight days instead of ten to twelve, and the disease produced was incomparably milder.

Inoculation was introduced into England by Lady Mary Wortley Montague, whose husband was at the time Ambassador in Constantinople. There is an interesting history of an extensive use of inoculation carried out by her grandson, William Stuart. While he was vicar of Luton, in Bedfordshire, a malignant smallpox epidemic broke out in that neighborhood and he, having absolute confidence in the practice, offered to have every person, who was uninfected, inoculated at his own expense. He had only a country practitioner and country nurses to depend upon, and above two thousand persons were inoculated. Only three people died; an infirm, unhealthy woman, a man past eighty years of age, and an infant whose mother afterward confessed she knew it had already caught the disease, which, in her ignorance, she supposed inoculation was to cure. For several succeeding years the smallpox scarcely reappeared in that district.

The only recent reference to inoculation which the writer has found is by Plehn, who describes the process as practised now in central Africa. The upper arm is used as the site of inoculation, and the contents of fresh pustules are introduced into incisions made with a sharp knife. The result is never a general infection with smallpox, but the formation of typical vaccine pustules which in no way can be distinguished from those produced by vaccination. In many cases a group of pustules formed around the site of inoculation, or scattered pustules over the entire body. He never saw a serious illness nor a fatal case.

Notwithstanding the mildness of the disease so produced, there is no diminution in the virulence of the virus which is produced in the lesions. A case of variola inoculata is just as able to transmit the disease in its most virulent form as is a case of variola vera. It was this which led to the prohibition of the practice in England. Circumstances may arise even now under which inoculation may be necessary, as when in the absence of any means for vaccination the exposure of unvaccinated individuals to the disease is inevitable.

Experimental Smallpox.—The most extensive study was made by Brinckerhoff and Tyzzer, in the Philippine Islands. They found that vaccinia in the monkey runs a course comparable to that in man, that no exanthem is developed, and that only the cytoplasmic forms of cytoryctes occur in the epithelial cells. The result of their study of variola inoculation shows that after skin inoculations, a local lesion which reaches its acme on the seventh day develops, and this is followed by an exanthem which in the majority appears on the eighth day after inoculation and has a duration of five days, the first two of which are employed in growth and the last two in healing. The regional lymph nodes show an enlargement on the fourth and are markedly enlarged on the fifth

day. The constitutional reaction occurs at about the height of the active phase of the primary lesion; that is, on the sixth and seventh days of the disease. The temperature reaction begins on the sixth day and persists for two or three days. The decline of the fever is by lysis. The extent of the exanthem varies greatly. In some animals only one typical lesion was present, while in others over a hundred were found. As in man, the exanthem shows a partiality for certain regions. The face was most often the site of eruption. The exanthem presents the same histological features as in man. The parasites are present in the same forms, but the nuclear inclusions, though constantly present, are much fewer in number than they are in man. Inoculations in the mucous membrane of the nose, mouth, and palate of the monkey were not so successful as in the skin. The constitutional reaction was less marked and a general exanthem developed in only 2 out of 19 animals used. As it seemed evident that the disease produced experimentally corresponded rather with variola inoculata in man than with variola vera, numerous attempts were made to produce the true disease. Thinking that the mode of natural infection was by the respiratory passages, smallpox virus in various forms was blown into the lungs, with the result, that a lesion was produced in the lungs which was followed by an exanthem which was more abundant than in the case of skin inoculation, but which occurred at the same time after the inoculation. The virus was also injected into the blood in a single instance without changing either the period of incubation or the character of the eruption, though it was more abundant.

It is evident from these experiments: (1) That the monkey alone of all animals experimented upon is susceptible to smallpox. (2) The form of disease produced by inoculation is allied to, if not identical with, variola inoculata in man. The period of incubation of six or seven days is shorter than in true smallpox; the initial stage (two days) is shorter, and the eruption is less abundant. (3) The monkey is not susceptible to that form of infection which in man produces variola vera. (4) The inoculated smallpox in the monkey confers immunity to both vaccinia and to smallpox.

With our present knowledge of smallpox it is not possible to advance a theory of the disease which conforms to what appears to be known and which is explanatory. Of the mode of infection we are ignorant. The hypothesis which seems most plausible and which is most generally held is that infection takes place by the reception of the air-borne virus on the respiratory mucous membrane. The organism increases in the favorable soil and produces a local lesion—the so-called protopustule from which the infection of the blood takes place. Blood infection is marked by a sharp onset, and the skin eruption is embolic in character.

There are objections to this view. In the 54 autopsies made in the Boston epidemic a most careful search was made for a lesion which could be interpreted as such a protopustule and it was not found. The period of incubation which should correspond to its development is without symptoms. It is possible that it might have been present and healed without producing symptoms or perceptible remains of a lesion.

If we can judge by the character of the protopustule which is produced by the inoculation of the skin, such a lesion in the lung would have produced symptoms. The lung tissue does not seem to be a favorable soil for the development of specific lesions. They are but rarely found in the bronchi and not at all in the lungs. In support of the protopustule idea, cases have been known in which accidental infection of the skin and mucous membrane has been followed by an eruption. But these seem rather to have been cases of variola inoculata than of variola vera.

Any theory of the disease must take into account the three forms: From the contents of a smallpox pustule in man there can be produced vaccinia in the rabbit and calf, variola inoculata in man and in the monkey by skin inoculation, and probably variola vera in man by infection in an unknown manner. We cannot explain variola inoculata by the site of inoculation. We know that in other diseases the course of the disease may be modified by the locus of inoculation, one locality offering a more unfavorable soil than another. The disease in the monkey is the same whatever site be chosen, and we do not know that it would be different in man. It is always assumed that the virus is contained in the skin lesions, and there is much evidence for this. They certainly contain virus which will give rise to vaccinia and to variola inoculata, which latter will in an unknown way give rise to variola vera, just as the latter will propagate itself.

We do not know when the general infection of the blood takes place. The general disturbance which the onset shows has been regarded as evidence that blood infection takes place at this time, and the general disturbance may mean that the organisms have at this time been destroyed in the blood and the toxin set free. It is not at all necessary to assume the existence of a protopustule, for in variola vera the entire stage of development may pass in the blood. We know nothing of what takes place during the stage of incubation. It is difficult to explain the eruption otherwise than as due to a deposit of the organisms in the skin by means of the blood. Their development in the skin is not incompatable with the assumption of blood immunity, for there they would be withdrawn from the action of the germicidal factors.

In the investigations of the blood made in Boston, the organisms were not found in the circulation. It was not possible, however, to examine the blood in the period of incubation at which time it seems that the blood infection most likely takes place. In examinations during the initial and eruptive stage, organisms were not found in the blood, nor did the inoculation of the cornea give a positive reaction. It would seem that purpuric smallpox must differ in some way from the general course, but in what the difference consists is unknown. It cannot be a matter simply of diminished resistance of the individual to the organism permitting an enormous increase, for there would then be transitions between the purpuric and the ordinary forms. It would be possible to explain it either by the assumption of absence of a general blood immunity, or of the destruction of the blood complement permitting an unlimited infection by streptococci.

Although bacteria can be excluded as a primary cause of smallpox,

they play a prominent part in its pathology. The writer is inclined to regard bacterial infection as more important in bringing about the fatal termination than the specific parasite. It is impossible to say to what extent the lesions in internal organs are due to bacteria and their products. Some of them, notably the changes in the blood and blood-forming organs, and those in the testicle, are probably specific, and due to the action either of the specific parasite or its toxins. The degenerative lesions are very much the same as in other infectious diseases in which there is a combined bacterial infection. There is analogy in respect to the importance of the part played by bacteria in the other exanthemata, notably in scarlet fever.

The immunity conferred by smallpox and vaccination is due to a bactericidal or germicidal property acquired by the blood serum (Sternberg and Reed, Beclere, Chambon and Menard). In the comparative study of smallpox and vaccinia in the monkey, the unexpected fact was developed that the immunity produced by vaccinia was stronger than that produced by variola inoculata. The vaccinal immunity protected perfectly against both vaccinia and variola inoculation, while that produced by smallpox inoculation protected from smallpox but only imperfectly from vaccinia. The study of the period of immunity development by daily inoculation and vaccination showed that the immunity produced by variola inoculata appears between the fifth and the eighth days and the exanthem develops in an immune animal. The immunity which is produced by vaccination in the monkey appears between the sixth and the eleventh days.

There are certain questions which present themselves. These relate, first, to the parasite and its life-history; second, to the interrelationship of variola vera, variola inoculata, and vaccinia; third, to the immunity and its mode of production; fourth, to the mode of production of the exanthem; fifth, to the mode of infection in variola vera. There is some knowledge on all these points; but there is yet lacking the chain which will so connect them that the disease as a whole becomes clear.

Symptoms.—The period of incubation has been more accurately determined in smallpox, owing to the suddenness of the onset, than in any other infectious disease. It is but rarely that cases suitable for this determination are found, and they are more apt to be sporadic. The exposure must be but once and for a short time. A sufficient number of such cases have been recorded by competent observers. All are agreed in placing the time between ten and twelve days in the great majority. Welch and Schamberg have seen cases in which it was sixteen days and one in which it was five and one-half days. Knecht reports one case of seven and one-half days. In general the length of the period of incubation is of no influence in determining the character of the disease. Zuelzer says that in purpura variolosa the period is shorter, being from six to eight days in 9 cases. In the 10 cases of this seen by Bancroft, the period could not be determined. Usually there are no symptoms, the individual being in perfect health.

The *initial stage* (the period between onset and the appearance of the eruption) is found in practically all cases, and forms one of the most

characteristic features; it is even more characteristic than the eruption, for this may be absent (variola sine exanthema) or atypical (purpura variolosa). The duration of the initial stage is usually three days. Bancroft found variations from this in 263 out of 530 cases. In 7 the initial stage was absent or the symptoms were so slight as to be unnoticed; in 26 it lasted for one day; in 91, for four days, and in 139, for two days. Analysis of these cases showed no relation between the length of the initial stage and the severity of the disease.

The *onset* is usually sudden and marked by definite symptoms, such as great depression, headache, backache, chill, and vomiting; occasionally it is gradual and accompanied by malaise, fugitive pains, and gastric disturbances. The severity of the initial symptoms varies, but there is little relation between the initial severity and the character of the disease, since very light cases may begin with stormy initial symptoms. Mild initial symptoms, as a rule, preclude the more severe forms. The depression may be marked; there is a feeling of weakness and giddiness, with disordered consciousness. It not infrequently happens that individuals found on the streets in this condition are taken up by the police as being drunk, and the true condition becomes apparent only when the eruption appears. The depression is much greater than in typhoid fever, for in the depression of smallpox the patient is unable to stand, or staggers as if drunk. When brought into the hospital, the face appears sunken and pale, the features expressionless, the extremities cold, and the pulse small and frequent. The patient gives the impression of one overwhelmed by a poison. Children frequently show the beginning of the disease by general convulsions. Other disturbances of the central nervous system are seen. Insomnia, in part due to pain, is common even in the mild forms of the disease. Somnolence, sometimes to the extent of coma, is seen, especially in children. Bancroft saw one child in the status epilepticus with constantly recurring convulsions for an entire day. Many patients complain of terrifying dreams, and will even try to keep awake to avoid them. Delirium is common, and is usually of the type seen in drunkards. In spite of the delirium the patient may be roused and made to answer questions. Sometimes the most violently delirious will suddenly become rational. Catatonia and sensory disturbances in the form of local anesthesia have been described. Bancroft saw disturbances of speech, exclusive of those incidental to delirium, in 3 cases—in 1 consisting of a slight stammering, and in 2 of a transitory aphasia lasting from the first to the fifth days.

Headache as an early symptom is common; it is usually severe and often sharp and agonizing to such a degree that patients make violent outcries and grasp at the head. It usually extends over the entire head, or may be confined to the forehead and temples. It is often described as though a band were encircling the head, or as a lancinating, throbbing pain. It may continue unchanged during the entire initial stage, and gradually subside as the eruption appears. *Backache*, usually localized in the lumbar region, is a well-known symptom. This has special importance in the early diagnosis because it appears in no other acute febrile disease so frequently or with such intensity. Sydenham com-

pared it to the pain of kidney colic. It may be accompanied by pain in the thighs, hips, bones, and joints, or extend over the sides and simulate the pain of pleurisy. Pain and stiffness in the muscles at the back of the neck are not uncommon. The pain may occur with the onset or in the last days of the initial stage, and usually disappears as the eruption comes out.

Gastric disturbances are common during this stage, at the onset in the form of pain, nausea, and vomiting, and later as anorexia and vomiting. The tongue is usually covered with a whitish-yellow coat, and bears the marks of the teeth; the breath is offensive. Injection and swelling of the tonsils and pharynx are often seen, and pain is complained of by the patients. In cases with pharyngitis there is apt to be a more extensive eruption on the mucous membrane.

Menstruation appears almost regularly in the initial stage, even when the regular period has not arrived, and is usually abundant. This may be of importance in the early diagnosis. In pregnant women miscarriage is common at this period.

A *chill* more or less definite in character usually marks the onset. The temperature rises rapidly to about 104° F. and remains at this height with slight morning remissions for about three days. In the lighter cases the temperature falls to normal at the end of the third day; in the more severe, the decline is gradual, and the return to normal not completed before the fifth or sixth day. With the fall in temperature the eruption appears, the full development of which is reached after normal temperature is established. In a case of moderate severity the temperature usually reaches the normal point two days after the beginning of the eruption. The pulse and respiration are increased in proportion to the degree of the fever. The urine at this time usually contains albumin and presents the characteristics common to febrile diseases. The spleen is variable, sometimes being enlarged, usually not. The initial illness may be so severe that the patient may die before the appearance of the eruption (variola siderans).

Prodromal Rashes.—The recognition of the appearance of rashes during the initial stage is of comparatively recent date. It seems hardly possible that they could have been overlooked by the earlier observers, and it has been supposed that they did not occur. Sydenham makes no mention of them; but then he did not clearly distinguish purpura variolosa from variola hemorrhagica, although he must have seen both types; nor did he distinguish varicella from variola. The rashes were seen by some observers who regarded them as due to mixed infection with measles or scarlet fever. The first description of the rash was given by Rembold in 1840. He says: "Cases are seen which have been regarded as a combination of smallpox with other diseases. I have observed cases of this sort at different times, and hold another view regarding them, namely, that they are not independent exanthemata appearing simultaneously with smallpox, but a condition of the skin which seems to introduce the smallpox eruption." The classical description of the rash is by Simon, in 1870. Its frequency varies greatly in different epidemics, but it is never common. Bancroft observed initial

rashes in 16 of the 1200 cases seen by him. The rash may be erythematous or petechial, and may last from a few hours to several days. The erythematous rash usually appears on the second day of the disease, reaches its full development on the third day, and finally disappears before the development of the specific eruption. The rash varies from a mere flushing of the face to a general erythema in which the entire body is of a bright red color. It is often faint over the lower extremities, even when intense elsewhere, and it may be mottled, alternating with areas of normal skin. The eruption may be composed of fine macules.

The second and the more common form is the petechial. It may occur alone or associated with the erythema. It may appear as a diffuse, dark red erythema, which only upon pressure discloses bright red round or oval petechiæ from 1 to 2 millimeters in diameter. Bancroft found the petechiæ to be numerous in scar tissue, particularly in the lineæ albicantes of the abdomen. The petechial rash lasts longer than the erythema. Its appearance changes rapidly after the third day, when the associated erythema disappears and the petechiæ become yellowish brown and at the end of the week generally disappear. The favorite seat of the petechial eruption is the lower abdominal region, together with the genitals and the inner surfaces of the thighs. With the patient lying on the back with the legs in contact, the affected area takes the form of a triangle, the apex of which is toward the pubes and the base crosses the abdomen transversely in the neighborhood of the umbilicus. It may also extend up the lateral surfaces of the trunk to the axilla, and from this point it frequently invades the axillary folds, the contiguous portions of the arm, and the pectoralis major muscle, forming the brachial triangle of Simon. Curschmann says he has seen a macular initial erythema around the nipples in women in cases otherwise free. The rashes are as common in men as in women, and have no prognostic importance. The fact that the petechial rash appears on parts of the body which are comparatively little invaded by the pock eruption has led to the idea that they protect the parts from the pocks; but there may be a full development of pocks in the region formerly occupied by the rash. There is another form of rash which develops late in the disease, within or following the period of crust formation. Bancroft observed this in a small number of cases, all of which, with one exception, occurred within a space of three months and near the close of the epidemic. According to Simon there is usually no increase of fever with the eruption, or it is slight. In most cases there is intense reddening of the fauces and swelling of the tonsils. Some of the cases of this which Bancroft has described depart so from the usual type that it is difficult to avoid the conclusion that they were instances of mixed infection with scarlet fever. Bancroft's cases occurred in the more severe types of smallpox, usually about the thirteenth day, and the rash was preceded by fever amounting to 104° F., headache, nausea, and vomiting in 7 cases. The eruption commonly appeared either with the rise of temperature or on the day following, and closely resembled scarlet fever. In the more severe cases the erythema was general; in the lighter it was localized on the abdomen, on the flexor surfaces of the arms, on the

legs, in the folds of the axilla, and on the groins. Its duration was ordinarily from two to three days, and it was followed by desquamation. One case which showed a rash on the ninth day of the disease, accompanied by fever on the ninth, twelfth, and fifteenth days, was discharged from the hospital on the twenty-fifth day, with desquamation incomplete. Eight days later a member of his family was admitted to the scarlet fever ward of the Boston City Hospital, with no known source of contagion. On the other hand, Bancroft, who was constantly exposed to cases of this sort, six months later, after the conclusion of the work at the smallpox hospital, contracted scarlet fever.

The end of the initial stage is marked by a decline of temperature, which may reach normal, and a general abatement of all the symptoms. The intellect becomes clear, sleep is restored, the headache and pain in the back cease, and the patient may possess a good appetite and normal digestion. In this we have another peculiar and characteristic feature of this remarkable disease.

Eruption.—This is preceded by a diffuse erythema most marked on the forehead. The eruption varies widely according to the part of the body involved and the thickness of the skin. Patients ordinarily notice it first on the forehead and wrists. Close examination may show a few macules on the abdomen before these regions are affected.

The lesion first appears as a small red macule 1 to 3 millimeters in diameter which in the beginning is slightly indurated. It becomes pale on pressure; on removal of pressure the blood quickly returns. A capillary pulse is often seen in the macule, and most readily immediately after the removal of pressure. Within the middle of the macule there appears a small gray spot which gradually becomes filled with fluid. It increases in size, chiefly at the periphery, so that the periphery rises above the level of the centre, producing a crater or umbilication. It becomes a tense hemispherical elevation, generally umbilicated, though it may be rounded, contains a gray transparent fluid, and is surrounded by a red areola. The pock gradually assumes a yellowish tinge, and by the eighth day of the disease it is filled with a distinctly puriform fluid. It is not possible to empty either the vesicle or the beginning pustule by a single puncture. The fluid is contained in a number of cavities within the epidermis, and these do not communicate until a very late stage of pustulation. Close examination of the beginning vesicle, using a magnifying glass in bright light, shows that it is composed of a number of very minute clear points which correspond to the single collections of fluid in the epidermis. From the climax of development shown by the large, tense umbilicated pustule, a gradual retrocession, beginning usually on the tenth day, takes place. The lesion becomes less tense, its fluid contents disappear, and it becomes converted into solid reddish-brown material. This for a time is closely adherent, but later separates and falls off as a flat, hard, circular disk of an average diameter of 3 millimeters. In the beginning the macule is usually slightly indurated, and with the increase of the exudation within the epidermis the induration increases. In both vesicles and pustules the induration is marked; it is distinctly circumscribed, and gives the impression of a shot beneath

PLATE XIX

Serial Photographs of Smallpox in an Unvaccinated Man.
Third Day of Eruption. (Welch and Schamberg.)

PLATE XX

Fourth Day of Eruption. (Welch and Schamberg.)

PLATE XXI

Sixth Day of Eruption. (Welch and Schamberg.)

PLATE XXII

Eighth Day of Eruption. (Welch and Schamberg.)

PLATE XXIII

Tenth Day of Eruption. (Welch and Schamberg.)

PLATE XXIV

Twelfth Day of Eruption. (Welch and Schamberg.)

PLATE XXV

Sixteenth Day of Eruption. (Welch and Schamberg.)

PLATE XXVI

After Recovery. Scarring Present, but Not Deep.
(Welch and Schamberg.)

the fingers. The development of the pock is accompanied by œdema of the corium and subcutaneous tissues. This is most marked on the face and eyelids, often causing complete closure of the eyes. The swollen countenance covered with brownish-yellow crusts, the closed eyes, the thick protruding lips dribbling saliva, and the uplifted hands, give a terrifying aspect to the patient.

In the lesions on the face the initial induration is more marked than elsewhere. The early lesion of the face is a papule often with a shallow depression at its apex. The evolution of the lesion is here more rapid than elsewhere, and the pustular stage more quickly reached, the climax of development occurring on the eighth or the ninth day. By the ninth day, in all but the lighter cases, an exudate appears upon the surface of the pock, consisting of a thick, yellowish material which soon dries into a gray or greenish-gray crust. When the lesions are close together this may completely envelop the face and harden into a tough brown mark. When the pocks are separated, the exudate in drying forms a disk upon the apex of the pock. Upon the scalp the lesions appear later than they do upon the face and may cause great pain.

Upon the hands the eruption is abundant, and the tension produced by the pocks and the accompanying œdema causes great pain. The pain is intense when the pocks develop beneath the nail. The patient usually assumes a characteristic attitude, elevating both hands, and spreading the fingers as widely as possible. When the horny layer of the epidermis of the hands is thick, the pock may pass through all of its phases without distinctly elevating the surface. After the absorption of the fluid of the pustule, large disks remain beneath the horny layer, which must be picked out before the patient is discharged from the hospital.

The eruption on the trunk is later in appearing than on the face or on the arms. It is usually less abundant on the abdomen and in the groins than elsewhere. It is profuse on the back, especially in its upper part, and here the lesions are generally accompanied by an extensive area of the erythema surrounding the areola, forming irregular rectangular areas, the long axes of which are parallel with the ribs. This erythema persists until the pustular stage is reached. In general the lower extremities exhibit the eruption later than any other part of the body, although a small area of pock formation may appear very early upon the inner aspect of the thigh. The leg from the ankle to the knee is often almost wholly free.

The lesions on the face dry first; next, those on the arms; later, those on the trunk and the lower extremities. In children, owing to the thinness of the epidermis permitting the fluid of the pock to come through, and owing to the greater tendency to injury, crust formation is more common than in the adult. The crusts of the individual lesions fall off, and sometimes the epidermis of the palm or the sole is cast off in one piece, carrying the disks upon its inner surface. Scars result when the lesions are sufficiently deep to destroy the papillæ. The extent and character of the cicatrix depend upon the depth of the lesion. In studying the healing lesions in every stage the writer never found any

regeneration of the papillæ. In severe cases the nails fall off, and in nearly all cases the hair is lost during convalescence.

The eruption on the mucous membranes is typified by that on the soft palate. It begins here, often before the appearance of any lesions upon the skin, with the formation of a papule. The papule develops into a vesicle which ruptures, forming a deep white erosion. The rupture takes place so early that in but one or two instances has the writer been able to find unruptured lesions at autopsy. The eruption is most abundant upon the soft palate, although the entire mucous membrane of the fauces may be affected.

The pocks may develop atypically. One of the most common variations in severe cases is delay in the evolution, whereby the pocks, which in lighter cases are well filled out and pustular by the eighth day, do not reach their full development before the twelfth day. Another atypical condition is seen occasionally toward a fatal termination. Instead of developing into full, rounded pustules, the pocks may remain umbilicated, or even flatten down, puckering in the centre, and presenting a dull gray instead of a yellow color. Not infrequently, and in cases which do not belong to the hemorrhagic type, the centre of the pock becomes dark red from hemorrhage. This is seen most frequently in the lesions of the forearms and legs. In certain cases the development of small vesicles is seen, which have nothing to do with the pock formation, but are due to the elevation of the entire epidermis by the œdematous fluid coming through. They vary in size from small foci, no larger than the beginning small pock vesicle, to large bullæ. They may be filled with clear fluid or the fluid may be dark from admixture with blood. The bullæ may occur in the midst of pustules, in which case these are elevated or split horizontally. Similar vesicles may be seen on the mucous membranes.

Any condition which gives rise to any irritation of the skin influences the eruption, probably by causing increased vascularity. The eruption is often peculiarly abundant on the neck, where the collar is worn; along the line of pressure at the waist; and, in women, where the garter is worn. In a musician there was an abundant eruption on the shoulder where the body of the violin rested. There have been many observations of an abundant eruption in areas of hyperemia produced by a mustard plaster or iodine. An area of abrasion of the skin produced during the stage of incubation was surrounded by groups of pustules. On the other hand, one patient came into the hospital with an antiseptic dressing around the foot and lower leg which was allowed to remain. There was a very abundant eruption elsewhere on the body, and a total absence of eruption in the area beneath the bandage.

According to the character of the eruption, smallpox has been divided into a number of varieties. Such a division is artificial and the varieties merge into one another by intermediate forms. The typical cases of each variety are, however, fairly distinctive.

Variola without Eruption.—This is the febris variolosa of Sydenham. In every extensive epidemic instances of this unusual form of the disease are seen. There is illness of an indefinite character, occurring chiefly

in nurses, physicians, and hospital attendants, who are rendered practically immune by their former vaccinations, on the twelfth day after exposure to smallpox. The symptoms are headache, pain in the back, slight fever, gastric distress, and nausea. These may be so slight that the individual pursues his ordinary work, or they may approach in severity an ordinary initial stage. The symptoms last two or three days and then suddenly abate. Numerous examples of this were seen at the Municipal Hospital of Philadelphia during the epidemic of 1901 to 1904, when a large number of volunteer nurses and physicians went to the smallpox wards to assist in caring for the unusual number of patients. In several cases the symptoms were severe enough to confine the patient to bed and in at least two instances an eruption was expected because of the severity of what was thought to be "the initial stage." Characteristic initial rashes may appear during the attack. One patient, a pregnant woman, remembered having a headache about two weeks after exposure to the disease, but was not otherwise affected. Her child showed a typical eruption when two days old.

Abortive Smallpox.—There is properly a distinction between this and the mild form, but the term is often used to designate both conditions. It includes those cases in which the lesions are numerous in the beginning, appear to be following the usual course, and suddenly abate. The initial stage may be mild or most severe, accompanied by delirium and unconsciousness, and continue for four or five days. The lesions may be smaller and more superficial than usual. The vesicle develops on the apex of the papule, never completely replacing it, and on the fifth and sixth days, instead of becoming a full, tense pustule, collapses and dries up, forming a thin brown crust which is soon desquamated. Such cases of abortive smallpox have an interest in that they have been confounded with varicella. This modification of the ordinary eruption is seldom manifested by all the pocks upon the body; more commonly certain lesions continue to develop into fully formed pustules, so that scattered among the abortive pocks are occasional typical pustules. The lesions of the lower extremities show the least tendency to modification.

Discrete Smallpox.—This is the ordinary form, and includes all those cases in which the lesions are not sufficiently numerous as to be confluent. Attacks in which the lesions are everywhere discrete usually follow a mild course. In 54 autopsies no cases with well-developed pustules were found in which there was not some confluence. The cases without confluence were those which died in an early stage before the eruption was fully developed, or those in which the eruption followed an atypical course.

Confluent Smallpox.—In this the eruption is so abundant that the lesions do not develop independently but merge into one another. Pustules may be very closely set and be seemingly confluent when they are not really so, the single lesions being separated by short intervals. Confluence takes place during the early active period of the development. From histological study it is evident that the development does not take place diffusely over a large area of the skin, but from single

foci which in the course of their development coalesce with those immediately adjoining. The confluence takes place in those parts where the eruption is usually the most abundant, most frequently on the face. The confluence may be apparent at the end of the first week. It is seen, next to the face, most frequently in the eruption on the ankles, on the dorsum of the foot, on the hands, and on the arms. In very severe eruptions the lesions may be confluent almost everywhere save on the trunk. The confluence undoubtedly signifies a more severe type of the disease. There is nothing in the confluence *per se,* it merely denoting a more abundant eruption and complete development. Sydenham calls attention to the importance which the abundance of the eruption on the face plays in denoting the severity of the case. It is rare to find a case of typical confluent smallpox in an individual who has been vaccinated. In the old epidemics the majority of the cases often followed this type.

Hemorrhagic Pustular Smallpox.—A tendency to hemorrhage in, and in the vicinity of, the pocks always denotes a grave form of the disease. The eruption in these cases is abundant, but fully developed pustules are not numerous. The contents of the pocks may be hemorrhagic, but the tendency to hemorrhage is best marked by the presence of petechiæ in the skin around them. Such petechiæ are seen chiefly on the face, legs, and arms. Small vesicles may be seen on the surface of the petechiæ. Bullæ with hemorrhagic contents are also found. Sydenham described these and recognized their importance in prognosis. He describes them appearing upon "a ground covered with innumerable pustules, conspicuous in size, and filled with a clear serum. When the vesicles were broken the skin underneath was black, and, as it were, mortified. Death was the lot of all those whom I ever saw with this fatal symptom." Such hemorrhagic cases seem to occur by preference in drunkards and in individuals weakened by antecedent disease. The tendency to hemorrhage is not confined to the skin, and there may be hemorrhages in the mucous membranes. Hematuria in both this and purpuric smallpox may result from hemorrhage in the pelvis of the kidney.

Purpuric Smallpox.—This is the most atypical and fatal form, and it is doubtful if a well-marked case ever recovers. It is doubtful if a sporadic case would be correctly diagnosed, particularly if the physician was unacquainted with smallpox. It departs so much from the ordinary type that its status as a definite form of smallpox was not established until the German epidemic of 1870. It is most apt to be found during an epidemic, but can also appear sporadically. The frequency varies. In the epidemic of 1901 to 1902 Bancroft found 12 cases in 1200. It is generally held that it occurs most frequently in young and robust individuals, in men more often than in women. In Bancroft's 12 cases recent vaccination had not been practised in any, although unsuccessful attempts had been made in 2 within the two weeks preceding the onset of the disease; primary vaccination in childhood had been attempted in 7, of which only 3, men of an average age of twenty-seven years, showed typical foveated scars; 3 were unvaccinated. The average age

was thirty-four years. The onset is usually stormy, with chill, nausea, vomiting, and intense headache. This is not necessarily the case; 2 of Bancroft's patients worked during the first two days of the initial stage. The fever at onset is, as a rule, not so high as in ordinary cases. Usually on the second day a superficial bright-red erythema resembling that of the initial rash appears, first on the chest, arms, and face. Within twenty-four hours this may spread over nearly the entire body, and is accompanied by marked increase in the constitutional disturbances. Severe deep-seated and agonizing pain is felt in many parts of the body, including the bones and joints, but is most intense in the precordium and epigastrium. The erythema changes from a bright-red to a dark terra-cotta color. Petechial ecchymoses appear in it and may present little contrast with the general dark color. In extreme cases the entire body takes a general dark plum color, on which the petechiæ and ecchymoses may be faintly seen. There is great œdema, especially of the face. In the mucous membranes the same tendency to hemorrhage is seen. There is bleeding from the nose, and the nostrils may be partly occluded by the crusts of dried blood. Bloody saliva, due to hemorrhage from the gums, trickles from the mouth; there is a cough with bloody expectoration. The tongue, though swollen and coated, does not show the same tendency to hemorrhage as the other mucous surfaces. Women have abundant metrorrhagia, and abort if they are pregnant. The urine is scanty, high-colored, albuminous, bloody, and contains blood-casts. The pulse is high and proportionate to the fever. In many cases death takes place before the development of any eruption. In some cases a few superficial vesicles on the face or elsewhere may be seen. In one of the most typical cases, the only evidence of the eruption was a few scattered vesicles around the ankles. Individuals who live until the fifth or sixth day may show the beginning of a typical eruption. The sensorium is clear even toward the last; patients may be drowsy, but they can be easily aroused and answer questions intelligently.

The relation of this form of purpura to smallpox is now no longer in doubt. It occurs only after exposure to the disease, and exposure to it may be followed by the typical disease. All doubt is easily set aside by the histological examination of the skin. This shows everywhere the earliest lesions preceding the formation of macroscopic vesicles. The foci are so numerous that had the disease progressed the entire body would have been covered by a confluent pock. In all of the cases examined by the writer, there was an intense streptococcus septicemia. There is no tendency for the disease to propagate itself; it may arise from and give rise to the mildest forms of smallpox. Death takes place at an average of between four and five days from the onset. It is rare that life is extended beyond the sixth day.

Fever.—The temperature curve in discrete smallpox is almost as characteristic as the eruption. There is a sharp rise at the onset, which is maintained with slight irregularities during the entire initial stage. It then falls, in some cases rapidly, in others by degrees, to the normal or a little above, and maintains this during the vesicular stage of the eruption. At the beginning of the stage of suppuration, at the end of

the first week, there is another rise, not so sudden as at the onset, nor does it ordinarily reach the same degree. The fever is maintained through the stage of suppuration until the beginning of desiccation, when it again falls in some cases rapidly, in others by degrees. There is much more irregularity in the second rise than in the onset. Fig. 22 shows a curve from a rather mild case of discrete smallpox.

There has been considerable discussion in regard to the pathology of the fever. Pfeiffer regards the first rise as specific and denoting the primary infection of the blood with the organisms which have entered from the hypothetical protopustule. At this time the organisms are deposited in the skin, where a second crop of organisms is produced, which again enter the blood and give rise to the secondary fever. There is not much in favor of this view. The onset of smallpox denotes the sudden action of a toxin. Not only the fever but the whole train of phenomena, especially those in the nervous system, seem capable of explanation by this view only. The writer is inclined to regard the primary fever as denoting not blood infection but immunity. At this time the organisms in the blood are destroyed and the toxin combined

Fig. 22

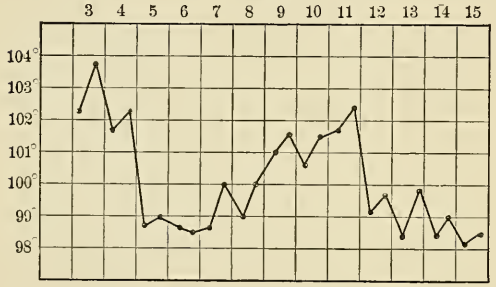
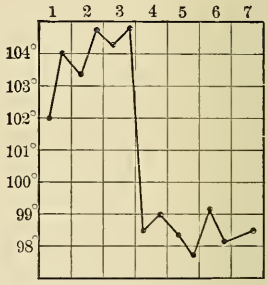


Fig. 23

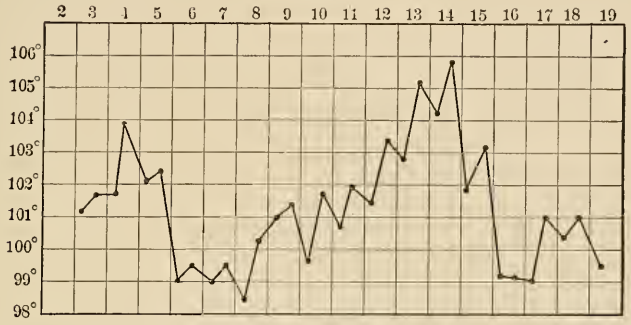


with them is set free. Those organisms responsible for the skin eruption have been brought to the skin before. This is in harmony with experimental evidence as to the time of immunity production and the infectiousness of the blood. No experimental study of the blood has been made during the stage of incubation. The blood is not infectious so far as can be determined experimentally during or after the initial stage. There is no warrant for the belief that the second rise is anything more than the fever of suppuration and due to absorption from the skin. Its curve is in no way specific, and the fever varies in degree with the severity of the pustulation. The secondary fever does not necessarily take place. Fig. 23 is from a case of mild smallpox with high initial fever and sudden fall. The low temperature was maintained during the course of the slight eruption.

While the fall of the secondary fever is generally by lysis, there may be a sudden fall as in the primary fever. Fig. 24 shows a case in which the high secondary fever fell suddenly in two days from a height of 106° to the normal. Fig. 25 shows a curve from a case in which there was a third rise coincident with the appearance of the secondary scarlatiniform

rash and which terminated fatally on the twenty-ninth day. The secondary fever, being due to the suppuration in the skin and the absorption of the products from this, will be influenced by the varying conditions of the suppuration. Both the degree and the duration of the secondary fever is in proportion to the severity of the skin lesions. In slight cases it may not last more than three to six days, while in severe confluent cases it may last six to twelve days and may merge into the fever due

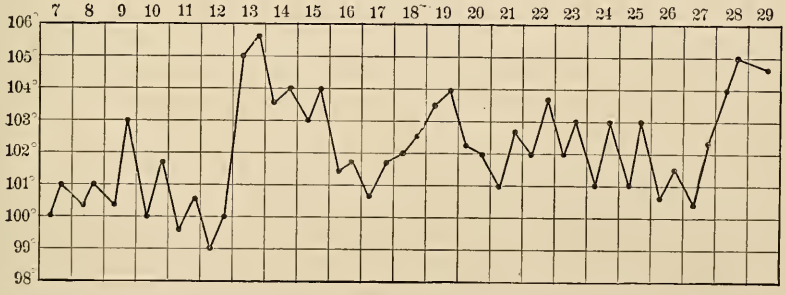
Fig. 24



to complications. In fatal cases there is often a high rise preceding death. In purpuric smallpox, the temperature neither in the onset nor in the course reaches the height observed in ordinary cases.

Not only the fever but the other phenomena of the suppurative stage denote toxic absorption. Delirium is common, not only in alcoholics, in whom the most violent forms are seen, but in other patients. This is also in great part dependent upon the severity of the eruption. Patients in delirium often strive to get out of bed and leave the hospital.

Fig. 25



The writer knows of an instance in which a patient, in the active suppuration of confluent smallpox, succeeded in leaving the hospital and wandered through deep snow to a small ice-pond into which he waded. He was found after a few minutes, returned to bed, seemingly none the worse for his bath, and made a prompt recovery.

Urine.—Arnaud found albuminuria in 95 per cent. of his cases, the amount varying from day to day. Roger found albuminuria not as common. It was present in 15 per cent. of the mild cases, in 25 per cent.

of the discrete, and in 28 per cent. of the confluent. Welch and Schamberg found albuminuria in 84.47 per cent. of the fatal cases and in 50 per cent. of the cases which recovered. In over half of the cases in which it was present it was discovered on or before the fifth day of the eruption. Tube casts were found more frequently in fatal cases than in cases which recovered. They also found, agreeing with Arnaud, that there is great irregularity in the character of the urine. The urine may contain albumin and casts for several consecutive days, then perhaps on alternate days, and then may be free for a week or thereabouts, with a return a few days later.

From our examinations of the kidneys, there was nothing to indicate any special influence exerted on them by the disease other than that due to the cytological blood changes. The degenerative changes were such as usually accompany acute febrile diseases and are associated with a varying degree of albuminuria. The cases of acute nephritis occurred late in the disease and were to be regarded as complications.

Blood.—There are certain rather characteristic changes and the examination, at certain periods, may assist in the diagnosis. During the febrile period the number of red cells and the amount of hemoglobin is practically normal or may be increased by the loss of body fluids. Postfebrile anemia is common, especially in severe cases, and poikilocytosis as well as variations in the size of the cells take place. During the febrile period the number of leukocytes remains normal or is but slightly increased; with pustulation a moderate leukocytosis (10,000 to 20,000) develops. The increase involves mainly the mononuclear forms. Myelocytes are nearly always present in severe forms, and may be found in mild infections as well.

Mild Smallpox.—From the oldest writers we learn that in early days, as now, there was great variability in the severity of different epidemics. Especially do they mention the unexplained and extraordinary mildness of certain epidemics. Welch and Schamberg quote Van Swieten (1759) as follows: "The primary fever is often little more than febricula and the pustules seldom exceed more than one or two hundred. The form is so mild that secondary fever is not manifested, convalescence coming on at the eighth day of the eruption." Sydenham (1771) described an epidemic of very mild smallpox and stated that "smallpox also has its peculiar kinds, which take one form during one series of years and another during another." Jenner was familiar with the mild forms of the disease. He wrote: "About seven years ago a species of smallpox spread through many of the towns and villages of this part of Gloucestershire. It was of so mild a nature that a fatal instance was scarcely heard of, and consequently so little dreaded by the lower orders of the community that they scrupled not to hold the same intercourse with each other as if no infectious disease had been present among them. I never saw or heard of an instance of its being confluent. The most accurate manner, perhaps, in which I can convey an idea of it is by saying that had fifty individuals been taken promiscuously and infected by exposure to this contagion they would have had as mild and light a disease as if they had been inoculated with variolous matter in the

usual way. The harmless manner in which it showed itself could not arise from any peculiarity either in the season or the weather, for I watched its progress upward of a year without perceiving any variation in its general appearance. I consider it, then, as a variety of the smallpox." Such an epidemic has prevailed in various portions of the United States for the past fifteen years. It is commonly supposed to have been imported from Cuba. It has been variously known as "Cuban, Philippine, or Texas itch." The disease was known to be contagious but was so extraordinarily mild that medical opinion was divided between its being a variety of chickenpox, a mild smallpox, or a new skin disease.

The mildness of such epidemics as those under discussion is best understood by a study of the mortality. In 1901 there were in the United States 38,506 cases of smallpox and 689 deaths (1.79 per cent.); in 1902, 55,857 cases, with 1892 deaths (3.31 per cent.); in 1909, 24,099 cases with 150 deaths (0.6 per cent.); in 1910, 30,352 cases, and 415 deaths (1.3 per cent.).

In this mild form the eruption may consist of a very small number of lesions which may attract little attention and the mildness of the constitutional symptoms as well as the inconspicuous character of the rash frequently cause errors in diagnosis until a severe attack is observed or a death occurs.

The initial period in such cases may be typical. The symptoms may be mild or severe. As a rule, there is a sudden remission of the symptoms with the appearance of a slight rash. Welch and Schamberg report an instance in which only a single pock appeared. The pocks are usually small and superficial, at times amounting to little more than red spots, and may be readily overlooked or their nature unsuspected. Inquiry of a patient with well-marked smallpox, often brings to light the fact that about two weeks previously another member of the household had been sick, who, upon examination, shows a few healed pocks. In one such case the crust from the "pimple" from a suspected individual gave the characteristic corneal reaction in a rabbit. In these slight eruptions the pocks are apt to be most abundant on that part of the body most subject to the eruption in well-marked disease. Some pocks are usually found upon the forehead, which may heal without leaving any perceptible scar. Usually an individual with a slight eruption of this sort is able to follow his occupation, and unless the pocks are fairly numerous upon the face, the disease is likely to be entirely overlooked. There can be no doubt that the disease is frequently spread by these mild cases. The habit of calling such cases *varioloid* has done much evil. The character of the disease in a second patient is not at all influenced by the character of the attack from which the infection is derived. Cases of confluent and purpuric smallpox are just as apt to follow infection from these mild cases as from any other form.

During the summer of 1912 one of these extremely mild epidemics, which was at first mistaken for chickenpox, occurred in Carbondale, Pennsylvania. The interesting feature, other than the lack of virulence, was the large number of unvaccinated individuals attacked (96) of a total of 97 cases in all. There were no fatal cases.

Histologically these mild cases present no differences from the same lesions in the severe forms. Both the protoplasmic and the intranuclear forms of the cytoryctes are present in the same numbers and relations. Such cases are now comparatively rarely found except in vaccinated individuals, as is evident from the descriptions of the disease in the prevaccination period and in the epidemics which take a mild course. The mild cases are certainly very much more prevalent toward the close of an epidemic than at any other time.

Fetal Smallpox.—This is comparatively rare, but undoubted. Infection may take place at any time after the fourth month. It may take place earlier and the fetus perishes and is expelled before signs of the disease are evident. The fetus apparently passes through the typical stages of the disease. It may pass through the entire disease *in utero* and be born with the resulting cicatrices and possess immunity; or the eruption may appear a few days after birth, or be perfectly developed at birth. There have also been cases apparently well substantiated in which the fetus has contracted the disease without infection of the mother. Such cases can be explained only on the assumption that the disease in the mother was so mild as to be overlooked.

Some of the cases regarded as fetal infection are not true infections. One such case occurred in our autopsies. The mother died on the thirteenth day of the disease and showed an abundant, partly confluent pustular eruption which was crusting in places. The child was well developed and nourished. The skin of the neck, shoulders, arms, chest, and back, presented small closely set elevations, from pin-point to half a millimeter in diameter, with a transparent vesicular centre and a white opaque border. The lesions were largest and most marked upon the backs of the hands. The general surface of the body was covered with a moderate amount of vernix caseosa. The general color of the skin was dull violet. The microscopic examination of the skin showed absence of true lesions. The vesicles were due to the elevation of the epidermis (or rather of the horny layer) by an exudation. The testicles and bone-marrow showed the lesions which the writer regards as characteristic. No cytoryctes were found in the lesions. The condition of the fetus was regarded as due not to a true infection, but to the action of toxic substances which developed in the mother.

The writer has examined the skin from two others, in which the lesions were typical and contained the parasites in the same relation as in the adult. There seems no doubt that the specific organisms can pass through the placenta. The character of the disease in the mother has no influence on the infection, though it has an influence on the life of the fetus. Infection of the fetus can take place as readily in a mild as in a severe infection of the mother. It does not take place synchronously with the maternal infection. It is not possible to accurately determine the date of the fetal infection, but it appears to be about two weeks after the maternal infection and to take place at about the period of onset. It is probable that at or just preceding the onset there is the greatest amount of infectious material in the blood of the mother. The general opinion is that the immunity acquired by the mother is

not transmitted to the child. Vaccination of children whose mothers had passed through the disease in pregnancy has proved successful in the majority of cases. There have been cases in which the infection of the infant has taken place at birth, the eruption appearing sixteen days afterward.

Complications and Sequels.—These are frequent, although none are peculiar to the disease but are such as we would expect to find in accordance with the character of the lesions. With the beginning of suppuration the specific character of the disease is over, but a suppurative process of great extent remains, usually with streptococci in the foci of suppuration. These foci offer favorable conditions for absorption and blood infection by the bacteria. Not only the skin but many of the mucous membranes are affected. No sharp line can be drawn between the complications and the sequels. We should expect to find complications due to the action of the specific toxic products of the cytoryctes. Most of these are included in the delirium and other symptoms of the initial stage. It is probable that there are others which appear later in the disease such as the specific orchitis.

Among the most common complications are *boils*. These appear most commonly after the stage of decrustation, about the third week, and add greatly to the suffering of the patient. They appear in crops and often have a very protracted course. It is unusual for a patient to pass through an attack of smallpox, unmodified by vaccination, without suffering from numerous furuncles. They are due in some cases to direct extension of the infection from the pustule, in others the infection takes place through the hair follicles from the surface. There may also be deep subcutaneous abscesses and diffuse spreading suppurations which may cause a fatal termination. The entire skin of the leg, arm, or scalp may be undermined. Septicemia due to this infection is by no means uncommon. Erysipelas is rare when we consider the opportunities for infection. Welch and Schamberg noted but 10 cases in 2000 patients. When it does occur it usually comes on after the third week.

Complications affecting the *respiratory tract* are common. The extensive, deep, and destructive ulceration of the larynx, which sometimes occurs, is usually fatal. In other cases the laryngeal lesions may produce cicatrices and deformities. Lesions in the lung are so common that they may be regarded as symptoms rather than complications. They are more common in the severe than in light cases, and consist chiefly of forms of bronchitis and bronchopneumonia due to streptococcus and pneumococcus infection. Lobar pneumonia is uncommon and is to be regarded as an accident and not related to the disease. In 54 autopsies it was found in 2 cases. Bronchopneumonia may be so extensive as to simulate lobar pneumonia. Pleuritis is met with occasionally but not nearly as often as one would naturally expect. Pleural effusion is less common than hydrothorax, due to nephritis or a failing heart. Empyema is uncommon and usually due to infection of the pleura from the lung and not to metastasis.

The *heart* suffers the changes which attend any severe febrile affection. Myocarditis is a complication in a very large number of cases,

particularly in the severe infections. Pericarditis and endocarditis are noted rarely. Phlebitis occasionally occurs during convalescence.

Chondritis, osteitis, and osteomyelitis are uncommon complications and are sometimes seen as sequels. Metastatic purulent arthritis occurs rarely and most often in children. The elbow is most frequently affected, and next the wrist.

Deep and superficial necroses of the soft palate and the pharynx occur, not accompanied by membrane formation; glossitis is occasionally seen, and less frequently noma. Parotitis occurs in a few severe infections. Thyroiditis is seen especially in young girls at or shortly after puberty. Bed-sores are not uncommon but less frequent than one would expect. Gangrene of the skin, often of considerable extent, may develop during the suppurative period in severe cases. It is usually superficial and seems to be due to the stasis of intense congestion. Many of the cases of extensive gangrene are fatal.

Complications affecting the *eye* are common. In the prevaccination days, blindness was a common result of severe attacks. Pock formation, though common on the lids, is uncommon on the conjunctivæ, though it undoubtedly occurs. The common conjunctivitis is due to the infection with pyogenic bacteria combined with the retention of secretion and circulatory disturbances brought about by tightly closed and swollen lids. The swelling of the lids is often so extreme that the eyes can not be opened. Ectropion may result from contracture of the cicatrices of the lids, which follow the pocks. When blindness results it is due either to corneal ulcers, which may perforate, or to pock formation on the conjunctivæ at the edge of the cornea. Marsten in reviewing 15,000 cases of smallpox stated that he found but 26 in which the pustule had been seen upon the conjunctiva. A true pock formation on the cornea does not take place, which is one of the best evidences of the dissemination of the organisms by the blood-stream. The writer has seen a true pock form in a vascularized cornea, which did not differ from the common lesions on mucous membranes. The external ear may be the seat of pock formation and the swelling may be so great as to completely close the external meatus. Otitis media is not common and occurs most often in the convalescing wards particularly in children. In a few cases thrombosis of the cerebral sinuses has followed but mastoid inflammation and suppuration during smallpox are rare.

Nephritis is not common, but albuminuria is found in a large number of cases. Nephritis is usually a late complication. Suppurative nephritis is infrequently found. Cystitis is rarely mentioned as a complication or sequel, but often occurs in very ill patients who do not empty the bladder completely. Orchitis, single or double, and usually accompanied by effusion into the tunica vaginalis, is rare and usually occurs during the pustular stage of severe attacks. Welch and Schamberg noted this complication in 8 of 2000 cases studied.

The complications and sequelæ affecting the *nervous system* are numerous, and have received much attention. An excellent account of them is given by Immerman. There is very little anatomical change found in the nervous system. Southard, after careful study of the cortex,

found no lesions. Focal lesions, consisting of hemorrhage and inflammation, have been described in both the brain and cord. The sudden hemiplegia and more partial paralysis which occur rarely in the course of the disease are to be attributed to such focal lesions. Affections of the cord are more common than of the brain, the most frequent being motor paraplegias. These are not confined to severe cases, but are nearly as common in mild attacks. They may appear in any stage and have been described as occurring in the stage of incubation. The paralyses occur suddenly; the bladder and rectum may be involved, but sensation in the affected area may remain. Cases have been described in which the paralysis assumed a rapid, ascending character, giving the clinical features of Landry's paralysis. Postvariola paralysis of the palate and pharynx has been described. It is unknown whether there was a mixed diphtheria infection in such cases.

Diagnosis.—This may be very easy or very difficult. There is little difficulty in the diagnosis of a well-marked case in the vesiculopustular or the pustular period. It is not possible to make a diagnosis in the initial stage unless one has a definite history of exposure. Even the most typical onset and initial stage may be paralleled by other acute febrile diseases. The prevalence of an epidemic or the history of exposure will awaken suspicion. In the intervals of an epidemic it is not likely that the initial symptoms would suggest smallpox unless the physician has a personal and extensive knowledge of the disease. The prodromal rash is not sufficiently common to give much help. A petechial prodromal rash occurring upon the abdomen below the umbilicus, and extending to the groins, on the second day after a sudden onset, with chill, nausea, and headache, is most suggestive when it occurs. The diagnosis can nearly always be made after the specific eruption occurs, even though the rash be scanty. There may be doubt between smallpox and *measles*. Apart from the history of preceding catarrhal symptoms and the presence of Koplik's spots in measles, both of which are absent in smallpox, and the different course of the fever, which in smallpox diminishes with the appearance of the eruption while in measles it increases, a careful examination of the eruption will decide. It must be remembered that the eruption of smallpox, even though it may appear in the beginning to naked eye examination to be papular, really is not so, but is vesicular. The vesicular character is usually most evident where the skin is thinnest, particularly on the scrotum. The use of the magnifying glass in a good light is often of material assistance in determining the vesicular character. The apparent papules rapidly become vesicles, while the measles eruption remains papular. The eruption of measles has a velvety feel and shows a distinct tendency for the lesions to arrange themselves in groups.

The hemorrhagic form of smallpox has been mistaken for cerebrospinal meningitis owing to the frequent presence of purpuric spots in the latter disease. An examination of the systolic blood pressure in such cases is helpful, for in meningitis one practically always has an increased systolic pressure, while in an acute infection, such as smallpox, the systolic pressure is normal or subnormal, providing one is not dealing

with complications. The greatest difficulty lies in differentiating smallpox from *chickenpox*. Even so accurate an observer as Hebra held to the unity of the two diseases. Both are vesicular and in both the lesion is in the epidermis. When the vesicles of chickenpox are completely formed they are more sharply elevated, rounder, and more translucent than in smallpox. The fluid is contained not in a system of cells, as in smallpox, but in a cavity that can usually be emptied by a single prick. This is a valuable sign. In chickenpox the lesions develop much more rapidly than in smallpox, and appear in successive crops. The vesicles usually remain with clear contents and do not commonly change into pustules. The lesions in the mucous membranes have much similarity in both diseases. No doubt should arise in differentiating between the florid eruption in the two diseases. It is in the beginning that doubt may arise. In chickenpox the vesicle arises on a hyperemic base which precedes it. There is seldom the hard, shotty feel of the vesicle in chickenpox which is so marked in smallpox, and which is due to fluid being enclosed in the small spaces in the epidermis. The initial stage of chickenpox is far less definite than in smallpox, is shorter, and the headache and pain are usually absent. Chickenpox may, notably in adult patients, begin with a chill and symptoms closely resembling those of mild and even severe smallpox. In chickenpox the first vesicles are nearly always on the body, especially on the back, while smallpox lesions appear first on the hands and wrists. As pointed out by Ker, the comparative immunity of forearm and hand from eruption in chickenpox is an important differentiating point. The presence of many lesions on the flanks, if the lesions are otherwise scanty, favors the disease being chickenpox. Welch has often called attention to the fact that in chickenpox the lesions are found on those areas covered by the clothing, while in smallpox the exposed surfaces were more commonly and primarily affected. The chief difficulty is in distinguishing between mild or abortive smallpox, in which the lesion remains in the vesicular stage, and chickenpox. These abortive or mild cases may have a very mild and almost or quite unnoticed onset and initial stage, and no more constitutional disturbance during the eruption than in chickenpox. In such cases a very close study of the eruption will usually decide. If not, the patient should be isolated and watched. The course of the eruption should decide, because even in the atypical cases of smallpox there is not so sudden and complete drying of the vesicles as in chickenpox, and the scab from smallpox is always firmer and more elastic than in chickenpox, which gives a granular, easily disintegrated scab.

Confusion has also arisen between pustular *syphilis* and smallpox. The diagnosis may be difficult without the aid of the Wassermann test when the pustular syphilide is well-marked and the smallpox mild, with pustules in full bloom. The presence or absence of slight fever will not decide, for though usually present in smallpox and absent in syphilis, the conditions may be reversed. In the course of twenty-four hours it is usually possible to decide, for in smallpox the eruption presents almost the same degree of development all over the body, whereas the rash of syphilis does not. The latter does not pass through the

typical vesicular stage of the smallpox pustule and does not change character so quickly. The characteristic adenopathy in syphilis is usually lacking in smallpox, although in the latter disease the lymphatic glands in many regions are enlarged. With expert microscopic aid it should be possible to make a diagnosis at once, for in the contents of the syphilitic pustule or in the scrapings from its base the *Treponema pallidum* will almost certainly be found.

Some have found difficulty in distinguishing between smallpox, *pemphigus*, and *impetigo contagiosa*. In pemphigus the vesicles vary greatly in size: there is little induration at the base, the covering of the skin is formed by the horny layer alone and is much thinner. In smallpox in the vesicular stage, while the majority of the lesions might resemble pemphigus, certain lesions will almost certainly be found in the papular stage and others in the pustular. In impetigo contagiosa a close examination with section into the pustule should decide and the same method will rule out *molluscum contagiosum*. They vary greatly in size and extent, and the lesion is in the corium and not in the epidermis.

Drug eruptions, particularly those caused by the salts of bromine and iodine, closely resemble the eruption of smallpox at times. The absence of constitutional symptoms, the irregular development of the rash, and the history of the patients, who have been taking drugs, aid in the diagnosis. *Herpes* and *acne* have rarely caused difficulty. The absence of symptoms and a study of the lesions is usually sufficient to make a diagnosis. Difficulty in diagnosis between acute pustular *glanders* and smallpox rarely arises. This form of glanders is unusual, and generally occurs in those whose occupation brings them in contact with diseased animals. In glanders abundant pustules may appear in the skin and show a similarity to variolous eruption. The patient with glanders is sicker than he would be with a corresponding smallpox eruption. The pustule of glanders is a true abscess of the corium, and the epidermis has no part in its formation. It rises as an abscess, is not so circumscribed as is the smallpox pustule, and beneath the finger feels more distant.

While the history and the fever may aid in the diagnosis of smallpox, only the eruption is decisive, and then only for one who knows the disease. There are two methods which decide the diagnosis, but they both involve delay as well as a trained opinion. One is by corneal inoculation on the rabbit. It is sufficient to prick the cornea with a needle which has upon it contents of a smallpox pustule or vesicle. In forty-eight hours there is a slight opacity at the point of inoculation, and on microscopic examination swelling and proliferation of the corneal epithelium, with numerous cell inclusions, is found. A more rapid and equally certain method is the direct microscopic examination of the suspected lesion. No other pathological process gives the same histological picture as the smallpox lesion, and no other shows in the cells the characteristic parasite inclusions.

Prognosis.—This is chiefly influenced by four factors: (1) The vaccinal condition. (2) The age. (3) The state of health, particularly as to the existence of chronic disease, at the time of infection. (4) The

type of disease. By far the most important is the vaccinal condition, for not only is infection in these vaccinated individuals comparatively uncommon, but the severe types of the disease are less frequent and the mortality much lower. The table from Welch and Schamberg's treatise on the "Acute Contagious Diseases" illustrates this point.

Mortality Rate of Vaccinated and Unvaccinated Patients in the Municipal Hospital of Philadelphia in Different Epidemics

	Cases.	Deaths.	Per cent.
1871 to 1872.			
Unvaccinated	697	449	64.41
Vaccinated	1629	276	16.94
Total	2326	725	30.75
1881 to 1885.			
Unvaccinated	447	252	57.37
Vaccinated	551	81	14.70
Total	998	333	33.36
1901 to 1904.			
Unvaccinated	1943	636	32.73
Vaccinated	1844	124	6.72
Total	3787	760	20.06

The above table shows how different epidemics vary in severity. In 1901 to 1904 the mortality rate among the unvaccinated is just one-half that observed in 1871 to 1872.

The statistics of the London Smallpox Hospital for the years 1838 to 1865 reveal that in nearly 6000 cases the fatality among the unvaccinated was 35.5 per cent. and in the vaccinated 8.7 per cent. More recent statistics of the Metropolitan Asylums Board for 1901 and 1902 show 9659 cases with 1629 deaths. Among 6945 vaccinated cases, including all degrees of vaccination, there were 705 deaths, or 11.5 per cent. In 2278 unvaccinated cases there were 753 deaths or 33.1 per cent. These figures are startling reminders of the frequency and fatality of an entirely preventable disease. Vaccination and systematic revaccination would have prevented the entire mortality and nearly all the morbidity.

The *age* of the patient is of great importance in the prognosis. It is unusual for an infant to survive an attack of unmodified smallpox, although in epidemics of a very mild character the mortality may be extremely low, even in infants. The mortality in children aged from one to five years is high, largely due to the fact that none of them are vaccinated. In the period from five to fifteen years the prognosis is better than in adult life. The mortality in patients aged over fifty years is always high, except in mild epidemics. The mortality of unmodified smallpox after middle life is naturally higher than in adolescence, as the immunity due to childhood vaccination is largely exhausted. Many patients after fifty have organic disease of the heart or kidneys which influences the prognosis.

The *general health* is an important factor in the prognosis. Among women the mortality is increased because of their liability to suffer

from uterine hemorrhages, or from miscarriage or premature delivery when pregnant. The occurrence of miscarriage or premature delivery apparently predisposes to the hemorrhagic form of the disease. In alcoholics the disease is likely to be severe and drunkards are predisposed to the more severe forms. Chronic disease of any kind adds to the seriousness of the malady. Especially is this true of pulmonary tuberculosis, myocarditis, and chronic nephritis.

The *type* of the disease and the extent and depth of the eruption are the most important factors (always excepting the vaccinal condition) in the prognosis. True hemorrhagic smallpox is practically always fatal. It is true that there is a modified form in which recovery sometimes occurs, but even in such cases the prognosis is not good. Next in severity is the confluent variety, the mortality of which is always high. Of 211 cases of this form seen in the epidemic of 1871 to 1872, by Welch and Schamberg, 168 died, a mortality rate of 79.62 per cent. In modified smallpox the mortality depends more upon complications than upon the primary disease. The character of the epidemic markedly influences mortality. The pandemic of 1901 and 1902 in the United States was characterized by a remarkably low death rate, but there were striking local differences. In certain sections the mortality was *nil*, while in others it was as high as among the unvaccinated in the old epidemics. Even in the prevaccination period the same differences in mortality were seen. Cases of mild smallpox and smallpox without eruption were seen then in certain epidemics as they are now. The decline in the mortality from that of the eighteenth century is due solely to vaccination and revaccination. There is no evidence that the disease is growing progressively milder.

The character of the initial stage may effect the prognosis. A mild initial stage is indicative of a mild form of disease. A severe initial stage may be followed by a mild form.

The prognosis is influenced by the type of eruption and depends essentially on the intensity and extent. Starting from smallpox without eruption and mild smallpox, in which the mortality is practically *nil*, there is a steady ascent to the cases of purpuric smallpox with an absolute mortality. The mortality in confluent smallpox is always high, averaging 60 per cent. It is not always possible to predict the character of the disease during the vesicular stage, for the eruption may be abundant, simulating the beginning of a confluent case; but the vesicles may dry up, very few of them become pustular, and the entire fever and other phenomena of the pustular stage may be absent.

There is no evidence that race has any influence on the prognosis. The disease has always been extremely virulent in aboriginal tribes; but in the unvaccinated everywhere the mortality may be high. In ordinary epidemics the mortality is high among the negroes; but these are the most careless in regard to vaccination.

All of the complications influence the mortality. Those due to extensive streptococcus infections of mucous membranes, with a possible septicemia following, are especially unfavorable. The prognosis in the individual case can best be determined by an accurate knowledge of

the extent and character of the disease and the effect it is exerting on important functions. The most lethal period of the disease is in the second week, at the height of the suppuration, and chiefly between the ninth and twelfth days.

Prophylaxis.—If each physician realized his opportunity, to mention nothing of his responsibility, in the matter of the vaccination and revaccination of each of his patients the civilized world would soon look upon a case of smallpox as a curiosity. Unfortunately, as a profession, we cannot but feel that we have failed in our duty when an epidemic of smallpox spreads through a community. It would be somewhat comforting if we could ascribe the fault for the absence of systematic vaccination and revaccination to the group known as antivaccinationists. This we cannot do. It is the indifference, or at least the lack of serious attention to the matter, of the members of the medical profession that allows an unvaccinated population to grow up. When every obstetrician feels it his duty to vaccinate the child that he has assisted into the world, and when every physician and surgeon is willing to preach and practise revaccination, there will be little need for smallpox hospitals. In every community where efficient compulsory vaccination is not carried out the appearance of a sporadic case of smallpox may easily lead to a more or less widespread epidemic.

We are probably correct in assuming that the infectious material resides in the eruption, that it may be carried through the air, to how great a distance we do not know; that everything coming in contact with the patient contains infectious material, and that this infectious agent may for a long time retain its infective power. The first step, therefore, is the prompt isolation of the infected person or persons. In unusually favorable circumstances (which are extremely rare) it may be possible to isolate the patient in a private house, but such a plan is beset with difficulties, and isolation is best conducted in a well-managed hospital whose staff is familiar with the management of the disease. It is even more necessary to isolate the mild than the severe cases of the disease, for individuals with very mild attacks are often not clinically ill, and often play an important part in spreading the disease, being unconscious themselves of any illness.

The ideal arrangement is to have a smallpox division as a part of a hospital for contagious disease. It should consist of simple barracks isolated from the other part of the hospital. In a large city, single cases of smallpox occur almost constantly, and should be cared for in a hospital which is in operation. There should be a capacity for unlimited extension during epidemics as long as no systematic policy of effectual vaccination and revaccination is in effect. Generally the smallpox hospital is used only in the event of an epidemic, and is unprovided with laboratories and opportunities for clinical and pathological investigation. Clinical teaching, the great stimulus to study, has no place in it. The energies of the physicians in charge are entirely taken up in controlling the exigencies of an unusual situation. The hospital should be used for teaching, because it is imperative that physicians should know the disease from clinical study.

The hospital should be provided with arrangements for taking charge of and detaining those who have been exposed to infection. Everyone who has been exposed should be vaccinated at once. If vaccination be performed immediately after the exposure, the vaccine immunity will develop in time to protect from the disease. It may be successful up to the fourth day after exposure, but rarely after this time. When vaccination is performed later, both vaccinia and smallpox run their course independently. The vaccination of these detention cases should be thorough, and repeated if unsuccessful. Suspects should be watched carefully, and isolated in case of any suspicious symptoms. If there is the least doubt at entrance the patient should be vaccinated and isolated until all doubt is removed. We do not know the life tenacity of the smallpox organism, and in the absence of this knowledge it is best to assume that it is as resistant as bacterial spores. All methods of disinfection should be so thorough as to destroy spores. Disinfection can be so thoroughly carried out that there is no necessity for the destruction of all articles which may have been infected.

Nurses and others in constant attendance on patients should be isolated, as it is possible that those coming into the infected atmosphere may carry infection to others. All such persons should have either a special entire suit of outer clothing or wear a gown over the clothing and cover the hair with a cap. Overshoes should be worn and discarded immediately before leaving the infected buildings. An exposed person should carefully bathe the exposed surfaces of the body before coming in contact with others.

The smallpox patient should be detained until all the infected epidermis is removed. We know that the dried disks contain infectious material. These will remain longer when enclosed in the thick epidermis of the palms and soles than elsewhere, and their artificial removal will assist in the cleaning process. The patient should then be scrubbed clean in a bath to which an antiseptic has been added and given clean (uninfected) clothing.

Treatment.—There is no specific treatment, but there are certain conditions which can be benefited and certain distressing symptoms which may be alleviated. It is doubtful whether, by means other than care and good nursing, the course of the disease can be influenced. With the great variations in the disease, it is easy to understand how methods of general and local treatment have arisen, been supported for a time, and then supplanted by others.

In many diseases a nurse in the sick room is a luxury, but in this disease she is a necessity if the patient is to be kept comfortable. In few diseases does the comfort, the future eyesight, and even the life of the patient depend so completely upon the faithful ministrations of the nurse as in smallpox. Most scrupulous attention to the cleanliness of the bed linen is necessary. The handling of the patient's body must naturally, covered as it is with suppurating lesions, be gentle, and the thought must constantly be how to accomplish what is necessary with the least fatigue and discomfort to the patient. There should be an abundance of air space, 2000 cubic feet if possible, a continual supply

of fresh cool air, and a low temperature, if possible. In no acute disease, unless pneumonia, is it so essential to have an abundance of fresh, air.

In the initial stage treatment is often necessary for the relief of headache as well as the body pains. Often these yield to mild measures, the application of an ice-cap or hot-water bag, but more often they require either small doses of caffein or phenacetin or what is more certain, moderate doses of Dover's powder. In severe attacks it is wise to have the head shaved. Removal of the hair early in the attack renders it comparatively easy to maintain cleanliness, while a much better opportunity is offered for necessary applications to the head. In nearly all severe attacks the hair is lost during convalescence even if spared in the beginning and the probability of a good growth of hair returning later is much increased by attention to the care of the scalp during the suppurative period.

The mouth and throat require almost constant attention during the eruptive stage. Sometimes, especially when there is much glandular swelling, the application of an ice-collar relieves the irritation of the throat. Mouth washes and mild gargles often relieve the patient for a short time. Drinks made from such substances as flax-seed, elm bark, or other demulcent herbs are relished if properly prepared and pleasantly flavored. Nothing can take the place of careful and frequent gentle cleansing of the mouth and throat. Small pieces of ice placed in the mouth of the patient at frequent intervals are often a great comfort. Orthoform tablets (1 grain) lessen the discomfort of swallowing and relieve the soreness. If there is intense pain on swallowing it is often necessary to spray the throat with a 1 per cent. solution of cocaine. When the odor from the mouth is disagreeable, the addition of carbolic acid or potassium permanganate to the gargles is useful.

During the early days of the attack the diet should be fluid, but as soon as the eruption has appeared a liberal, nourishing, light diet should be allowed. Water should be given freely.

In cases of delirium and great nervous excitement warm baths are very helpful and may be continued for hours and even days with benefit. Sponging with cool water or alcohol and water is often refreshing during the febrile period. Two hot sponge baths daily are necessary as a rule throughout the attack. An alkaline fever mixture is useful. Insomnia is often disturbing, and is usually due to the irritation of the skin; it is best controlled by opium derivatives, preferably Dover's powder.

It is most necessary that the eyes shall be frequently bathed with weak antiseptic solutions. Saturated solution of boric acid or very dilute solutions of bichloride of mercury are the most useful for frequent use, but weak solutions of the silver salts are frequently helpful. Vaseline or other ointments must be applied frequently to the lid margins to prevent them adhering together and retaining pus. When there is a profuse discharge from the conjunctivæ the application of the solid stick of silver nitrate must be done daily. Constant watchfulness for corneal ulceration is necessary, and if this occurs the pupil should be widely dilated with atropine. Hot applications are essential and the faithfulness with which these are applied is secondary in importance

only to the early recognition of the condition. Many eyes are lost because of the general toxemia. The entire cornea sloughs and it is often necessary to enucleate the organ. Small ulcers of the cornea often yield to care and treatment. The application of an ointment of hydrarg. ox. flav. (gr. ij, gm. 0.13), atropine (gr. iv, gm. 0.25), vaseline (ʒij, gm. 8) is often efficacious, applied to the eyelid twice daily. The frequent cleansing of the eye is the most important part of the treatment.

To quiet violent delirium it is often necessary to give opiates freely. Large doses of morphine hypodermically, repeated frequently if necessary, are often the most efficient remedy. Chloral and the bromide salts are of use, but are secondary in usefulness to the opium derivatives. In severe attacks it is necessary to force the nourishment and often to use stimulants as well. There is and will probably always remain much difference of opinion regarding the value of alcohol in such cases. It is not to be used as a routine measure, but is often an invaluable remedy.

In the true hemorrhagic forms there is little hope of recovery, but the patient must be given every care with the hope that the usual outcome will not result in that particular case. Considering how successful the treatment of certain obscure hemorrhagic conditions, notably hemorrhagic disease of the newborn, has been by the subcutaneous use of human or other blood serum, and considering how hopeless the condition is, it seems wise to try the effect of injections of blood serum.

For the average patient, after the initial headache and body pains are relieved, it is local rather than general treatment which is important. The eruption is usually distressing, although there are great variations as to the discomfort. It is important and often most difficult to avoid traumatic disturbance of the eruption. The itching is usually intense, and this is particularly true toward the end of the suppurative stage. At this time both adults and children, but particularly the latter, must be watched, and if necessary restrained from doing serious injury to the skin lesions by scratching or rubbing. It is often wise to bandage the hands of children so that they cannot scratch the lesions.

The local application of cloths thoroughly moistened with cold water and frequently changed seems to give the greatest comfort to the average patient. Tincture of iodine (10 per cent. in glycerin) painted upon the skin every other day until there is considerable irritation seems to hasten the maturation of the pocks and certainly renders the patient more comfortable early in the attack. In some patients it is necessary to use more dilute solutions of iodine, as the drug may give rise to a cellulitis. From the time the pustules mature the hot bath is the greatest comfort to the patient. Antiseptics and deodorants are often added to the bath with benefit. The crusts soon loosen and the pus is easily removed without pain. Linseed, starch, or other poultices are often of use in softening the more persistent crusts, and hot baths containing carbonate of soda, frequently repeated, aid in the same purpose. The application of soothing ointments relieves the irritation of the skin and softens the dry scabs. The hardened bits of epithelium in the palms and soles called "pits" and "seeds" are best removed, after thorough softening, by the use of some sharp instrument.

CHAPTER XXIII

VACCINATION

By GEORGE DOCK, M.D.

Definition.—Vaccination is the inoculation of vaccinia, by means of the virus of cowpox, and has for its object the production of a pock, with general symptoms, followed by more or less complete immunity against smallpox.

History.—The practice of vaccination we owe to Edward Jenner.[1] Under the name of cowpox certain diseases characterized by vesicular or ulcerating lesions on the udders of cows have long been known in England, and under corresponding names in other countries. The name was not limited to a single disease, but applied to various diseases that have nothing in common but vesicular lesions. In some cases, however, the disease has the characteristics of inoculated variola or vaccinia; it spreads from cow to cow in dairies, and when it once enters a stable usually affects the majority of the animals unless they are immune from a previous attack. Jenner originally supposed that cowpox was derived from "grease," a disease of horses' heels, and that, transferred by dairymen who dressed the horses' heels and also milked cows, the virus became more fixed in the cows.

As regards the cowpox, the probability is that this, in its specific form, is variola, derived directly or indirectly from human sources. The term "spontaneous" applied to some cases of cowpox is a bad one, since there is no reason to think that cowpox arises spontaneously any more than smallpox. As a rule the source cannot be found; but if we remember the tenacity and the wide spread of smallpox, the relation can hardly be doubted. Numerous experiments show that, while failures occur, it is comparatively easy to infect many species of animals with variola or vaccinia.

It was known to dairy-workers long before the time of Jenner that cowpox protected against natural or inoculated smallpox. In various parts of the world, at different times, a number of persons made experiments with the inoculation of vaccinia in order to protect againt smallpox. None of these detract in the least from Jenner's claim to immortality, for none of them led to a wide or general use of vaccination. Although his observations and experiments were few in number, they were more numerous than those of his forerunners, and were carried out with a scientific accuracy far ahead of the contemporary knowledge of infectious diseases. Formerly a rare operation, Jenner made it of world-wide use,

[1] "The Works of Edward Jenner and their Value in the Modern Study of Smallpox," by George Dock, *New York Med. Jour.*, Nov. 29 and Dec. 6, 1902.

and showed the possibility of carrying the virus through the human body and becoming independent of natural cowpox, an essential step in the development of vaccination.

Jenner's first work, *An Inquiry into the Causes and Effects of the Variolæ Vaccinæ*, appeared in the summer of 1798. Its reception at first was lukewarm; but a controversy soon sprang up and Jenner published additional observations and conclusions early in 1799. From this time progress was rapid. Before the end of 1799 several institutes for cowpox inoculation were established. In 1800 the operation was carried out in most parts of Europe and in America, where Waterhouse, of Cambridge, had taken it up with enthusiasm; and it was used very early in the world-wide Spanish colonies.

Very early Jenner established the following points: The protection of vaccination against smallpox, whether acquired in the natural way or by inoculation; the importance of using virus only from typical and regularly progressing vesicles free from suppuration or other complications; the advantages of a clean and simple operation; the possibility of partial or complete failure, with the indication for repeating it (or in case of need even variolating); the importance of special knowledge, experience, and careful observation in all cases. He realized that severe local lesions do not indicate protection, but may even be harmful. Jenner's great error was his belief in the life-long immunity conferred by vaccination; and yet if it had not been for this fallacy he probably would never have given vaccination to the world. The consequences of the error have not yet been overcome by the medical profession; but for this Jenner should not be held responsible.

Coincident with the rapid spread of vaccination was a marked fall in the extent and mortality of smallpox all over the civilized world. As an example, in London in the years 1761–1800 the mortality in the successive decades was respectively 24,234, 20,923, 17,867, 18,477. In the first two decades of the nineteenth century it was 12,534 and 7856. Toward the end of the second decade of the nineteenth century smallpox began to increase, and in some countries became almost as prevalent as it had been before. The causes of the recrudescence are not difficult to understand. Many people had been vaccinated so long before that they had lost their immunity wholly or in part. This was the time to settle the question as to the life-long protection which the early vaccinators so fondly believed in, but prejudices were still too strong. Many other people were not vaccinated at all, because smallpox was so much less frequent that the operation seemed unnecessary, and there was a smaller proportion than before not protected by smallpox. Smallpox virus existed in many places. No efficient effort had been made to stamp it out, and it was even kept up by sporadic variolation, not prohibited in England until 1840, five years later than in Prussia. Whenever the disease prevailed some vaccinated people were sure to take it, and many were the efforts to reconcile this with the sweeping claims of the early vaccinators. Imperfect vaccination, degeneration of lymph, new types of disease, the cowpox not the genuine kind, or the smallpox not real smallpox—such were the explanations made; but the practical lessons

were very slowly taken up. Looking back it is clear that certain great changes had occurred in the smallpox situation since Jenner's discovery. The absolute mortality was less; the disease was not so frequent as before in the years following the usual age of vaccination; and these facts were most obvious in countries that had the most thorough vaccination. The change in the age-incidence is interesting. Smallpox was commonly spoken of in Germany in the prevaccination days as "Kinderpocken." Of 1252 cases of smallpox before vaccination 94 per cent. were in children less than ten years of age, and no case above twenty. Of 1677 cases after vaccination only 18 per cent. were under ten years of age, and 42 per cent. over twenty. Epidemics were smaller, and mild cases, long known but rarely mentioned, became relatively more frequent. The recognition of varioloid as a mild but genuine form of smallpox was a great advance over the time not long before when each variety of smallpox was looked upon as a distinct disease, not protected against by vaccination.

In this period revaccination began. Suggested early in the century, it was long neglected. Certain German states first applied it to their armies. Würtemberg, after a trial in 1829, made it obligatory for recruits in 1833; Prussia in 1834. Some other German states did not adopt it until the 60's.

The most striking test of the possibilities of vaccination was made in the war of 1870–71, and depended largely upon the far-sighted care of the German military authorities. Smallpox became so prevalent in France in the preceding winter that efforts were begun to combat it, but the outbreak of the war not only prevented such action, but as usual caused a great increase of the disease, which rapidly extended over Europe. In Germany, where many prisoners of war carried the infection, the disease was widespread; but it was a striking fact that the German soldiers were not only less frequently and less severely affected than the French, but that they were less affected than civilians of military age in the same towns. The only difference was that all the German soldiers under arms at the outbreak of the war had been revaccinated within two years. The following figures show the mortality of different classes at that time: revaccinated 5 per cent., once vaccinated 14 per cent., unvaccinated 45 per cent. This object lesson was not lost on the newly formed German Empire. In 1874 the first law was passed providing for the vaccination of every child before the end of the second year, and of all school-children in the twelfth year. The result of the operation was to be a matter of record, and failure to produce a satisfactory vesicle necessitated a repetition. In the civil population the mortality sank rapidly, so that in 1910 the deaths in the whole empire were only 33 (15 being foreigners).

In the meantime other important events had taken place. The continued existence of smallpox was ascribed to degeneration of lymph, and this was sometimes obvious in the poor development of the vesicles. This led to efforts to obtain stronger virus. Cowpox had become very rare, and though rewards were offered in some countries, few cases could be found. Retrovaccination, or the inoculation of the cow with human

virus, was used to revive the stock, but not with the desired success. Numerous experiments demonstrated that vaccinia is variola in the cow. Inoculation of calves with smallpox material, with proper care, produces a disease indistinguishable from primary or "spontaneous" vaccinia, and giving the same protection against both smallpox and vaccination that natural cowpox gives. The contradictory results of the oft-cited Lyons commission, which believed that variola inoculated into animals remained variola, with all its dangers, are now universally believed to have been based on technical errors. Inoculation of the first remove of such material is likely to produce severe effects, such as intense local reaction, general eruption with secondary fever, or even death (Chauveau). But after several transfers through cows the contagious character is lost, secondary fever does not follow inoculation, and the material can be made to retain its characters without bad results.

Etiology.—Since vaccinia is then believed to be smallpox, altered by its passage through the cow, the etiological factor must be the same, modified in virulence if not in morphological characteristics. And in fact the history of the search for the cause of vaccinia is part of that of smallpox. Like the latter, vaccine has been investigated by all known methods for specific bacterial forms, but none have been found. Finally, after various indefinite alleged parasites were found, the bodies first clearly described by Guarnieri, called by him *Cytoryctes variolæ seu vaccinæ*, have been identified by all who have repeated his observations, although all have not come to the same conclusion as to details or biological position. In the United States Councilman (1903) and his associates have made important contributions.

The bodies are found in the inoculated cornea, skin, and mucous membrane, as early as sixteen hours (cornea), and are then of small size. They become more numerous and at the same time increase in size, and in course of time are found farther away from the point of inoculation, but also smaller than the older ones nearer the centre. In the smallest forms details of structure cannot be made out. They occur in the cytoplasm of epithelial cells, and also occasionally between cells. The smallest bodies are about 1μ in diameter, and stain more intensely than the cells. So far no specific stain has been discovered. Slightly larger forms are found often near the nucleus of the cell, or in the perinuclear space. As the bodies increase in size the structure becomes complex. A deeply stained granule can be seen within the body. As it becomes larger an unstained area appears surrounding the granule. In the rabbit's cornea at this stage the body measures from 5 to 7μ to 10 or 11μ in the skin and mucous membranes. In the calf the bodies are smaller, rarely exceeding 4μ. The smaller forms vary much in outline; the larger ones are usually rounded or reniform. The central granule stains like chromatin. No nuclear membrane can be demonstrated.

After the body has reached a relatively large size the chromatin is more abundant and irregular. It may appear as a mass of granules, and in later stages the granules are separate and distinct. In other cases the granules are in the periphery of the bodies, within small masses projecting from the surface, and resemble mulberry forms or segmenting

bodies. Other forms are found, suggesting segmentation, with a residual body. Cells containing the bodies are larger than normal, and "glassy," later vacuolated and hollow; but similar changes occur in cells not containing the supposed parasites. The nuclei of the cells may present various kinds of degeneration. Tyzzer excluded the possibility of error by confusion with degenerated red blood corpuscles, leukocytes, centrosomes, extruded nuclear material, and degenerations such as are caused by various infections. The morphological grounds for looking upon the bodies as organized parasites seemed to the early investigators very strong, though the supposed parasites did not agree closely with any known protozoa, except in pictures, and the latter do not lead to conviction any more than the very similar ones presented by various observers in cancer.

Ewing[1] (1904) came to conclusions at variance with those who believed in the protozoan nature of the bodies. He first made an effort to distinguish between vaccine bodies and other cell changes, and next to ascertain the differences that exist between vaccine bodies as found in rabbits and man, and those produced in other animals that may react to vaccine. In a preliminary study of material from autopsies on thirty cases of variola he found the vaccine bodies, but concluded they were probably cytoplasmic structures. Still later he gave strong reasons for the view that the Guarnieri bodies do not resemble endoglobular parasites as much as they do certain forms of cell degeneration with the formation of "chromidial bodies," explained by a separation of the chromatin from the achromatic substance of the cytoplasm, under the influence of toxins.

Since then the investigations have entered another phase. As early as 1904 Bosc and later von Prowazek described small coccus-like bodies in the protoplasm of the cells containing Guarnieri bodies in vaccinia as well as variola. The observations have been confirmed by many others.[2] Various observers differ as to the size of the small bodies, but von Prowazek makes a strong case for the identity of all that have been described. They begin as oval or rod-like bodies $\frac{1}{4}\mu$ long, but vary from that up to 1 and $1\frac{1}{2}\mu$. They show two points that stain with the usual nuclear dyes. The bodies occur not only in the cells, but also free. Similar bodies have been found in horsepox (Bormans) and sheep-pox (Paschen). These "initial bodies," as von Prowazek called them, divide like cocci. They show in fresh preparations a motion that some think active, others passive. Their small size makes it more likely they are the cause of vaccinia and variola than the cytoryctes. The virus is capable of passing paper, asbestos, and Berkefeld filters, which the Guarnieri bodies are too large to do. The latter can also be injured chemically, without destroying the specific character of the virus. According to the present view, developed chiefly by von Prowazek, the initial bodies are the earliest visible forms of the variola or vaccine virus. From them the Guarnieri bodies develop. The latter represent a specific reaction to the virus, caused by the irritation that the latter sets up in

[1] *Journal of Medical Research*, 1904, xii, 509.
[2] Galli-Valerio, *Centralblatt f. Bakt.*, 1912, Band lxiii, orig., pp. 53, 303.

the cells of the host, and formed partly from cytoplasm, partly from chromatin. The virus lives in symbiosis with the cells. Von Prowazek[1] assigns the germs to a group of protozoa that he calls Chlamydozoa (chlamys, a mantle), and in this group includes the causes of rabies, scarlatina, and trachoma.

The work of a number of investigators who oppose the theory of Guarnieri need not be quoted in detail. Suffice it to say that none of them, the most notable being Salmon (1897), Hueckel (1898) (who thought the bodies specific for vaccine, but not organisms), Roux, Borrel, and Sikorsky (1903) have successfully controverted the statements of the others quoted. Ishigami (1902) thought he had cultivated the parasites in a special medium containing epithelial cells.

Although bacteria are no longer believed to be the specific agents of vaccine, they are of great importance in the pathology and still more in the practical application of vaccinia. Lymph from young intact vaccine vesicles is sterile, but in lymph as ordinarily examined, bacteria of various kinds may be found, both in the calf and in the human vesicle. Most of them are harmless saprophytes, but pathogenic forms are not rare, though usually not very virulent, as the great majority of vaccine operations prove. Streptococci are rare, but have been found in the benign vaccine pustules in children.

Histology.—The investigations of Pohl-Pincus (1882), Unna (1882), and others, and more especially the studies by Howard and Perkins,[2] give us a fairly clear idea of the histology of the vaccine lesion. It begins as a hyperemia which increases in the purulent stage. Degeneration of epithelial cells, with swelling and vesiculation or reticulation, occurs, especially in the middle part of the prickle-cell layer. The remains of the puncture, if one has been made, show as a cleft filled with blood corpuscles, broken-down cells, and fibrin. Necrosis of cells forms columns that run down through the centre of the lesion, and the dropsical degeneration begins near these. The prickle-cells become smooth. At the end of twenty-four hours the epithelium shows swelling, but not macroscopically. Howard and Perkins found vesiculation far advanced at forty-eight hours. The reticulum, made up of fine and coarse fibers, can be traced to hyaline fibrinoid degenerated epithelial cells.

As the process advances, hydropic degeneration affects all the layers of the epithelium, and may extend to the corium. Nuclear changes then become more prominent, with numerous mitoses, often atypical, and with various forms of degeneration of the chromatin. At the margins of the vesicle the cells are often swollen and their prickles lost. Cell inclusions may be seen. Red-blood corpuscles and leukocytes occur in the degenerated tissue at the base and sides of the vesicles, eosinophile cells being often numerous. Changes in the corium are more marked than in variola. Œdema, leukocyte infiltration, and vascular changes, are described by Howard and Perkins. The sweat ducts and hair follicles

[1] *Arbeiten aus dem Kais. Ges.-amt.*, 1905, Band xxii, p. 534; 1906, Band xxiii, p. 525; 1907, Band xxvi, p. 54. *Münch. med. Wchnschr.*, 1909, No. 13, and von Prowazek und Yamomoto, ibid., 1909, No. 51.

[2] *Journal of Medical Research*, 1905, vol. xiv, No. 1.

are often unaffected by the dropsical degeneration, though polynuclear cells appear in them, and the ducts, with the degenerated cells along the seat of inoculation, show as strands among the hydropic cells and account for the umbilication. By the fourth or fifth day in the calf (Steinhaus), the fourth in man (Howard and Perkins), the vesicle ceases to increase in diameter, but becomes elevated from liquefaction of its contents. In the liquid contents are broken-down cells, free nuclei, and debris. As the epithelial cells liquefy, a gradually increasing immigration of leukocytes takes place, from about the third day, causing the contents to become turbid and purulent, and obscuring the histological features of the lesion. On the sixth day the pustular change is complete; the cellular strands begin to break down. On the fifth, sixth, or seventh day desiccation begins. The epidermis grows in from the sides, with numerous nuclear figures, gradually raising up the scab.

Howard and Perkins could find no bacteria in the lesions they examined from the second to the seventh day, and they conclude that mixed infection with bacteria plays no part in the production of the lesions of human vaccinia when the operation is carried out under proper precautions. These observers conclude that the degeneration and exudation "are due to the action of a powerful soluble toxin which acts very much like diphtheria toxin. It would appear that immunity production is intimately associated with the setting free of this poison in the lesion, for the œdema and other inflammatory changes persist long after the process in the epidermis has ceased to extend."

The Vaccine Virus.—Until late in the 19th century vaccine virus was derived chiefly from human vesicles and either used at once—"arm-to-arm"—or preserved in various ways. Sometimes the "crusts" or scabs were used, but must have been unsatisfactory, as they represent a stage of the lesion when specific activity is less and contamination greater than in earlier phases. Arm-to-arm vaccination in general gave good results; but it was difficult to keep up the supply regularly except in large cities, and even there the usual sources of lymph—foundling asylums—offered obvious risks. The difficulty of maintaining the supply and the danger of transmitting other human diseases made it comparatively easy to return to bovine lymph. Retrovaccination, or the inoculation of cows with vaccinia, had often been resorted to in order to improve strains of lymph. The virus was inoculated after the various methods practised with human lymph, arm-to-arm vaccination being imitated by taking the calf with ripe vesicles to the house of the patient, or making direct inoculations in a central locality. This method was abandoned only a few years ago. The use of ivory slips or "points" with lymph represented a great advance over other methods.

For various reasons, chiefly technical, vaccine "pulp" took the place of lymph soon after 1880. Pulp is the whole lesion, consisting of epithelial cells, leukocytes, red-blood corpuscles, fibrin, fat, specific and non-specific microörganisms, and debris. The use of pulp is often objected to, but without good reason. It is said to contain more pus and more bacteria than lymph, but pus should not be present in the vesicles when they are made into pulp; and it has not been demonstrated that the whole

lesion contains more bacteria than an equal quantity of the liquid. The so-called lymph was often largely blood-serum; but even pure lymph has not been shown to exceed pulp in specific action. If the prevailing views of the cause and histology of vaccinia are correct, pulp must be superior. At present the bacteria can and should be controlled, no matter what part of the material is used.

The animals used for the production of vaccine are calves or heifers, females being generally preferred, and light-haired ones on account of their clearer skin. The age is usually three to six months, though it varies from one month to two years. The animals should be sound and well, and, in order to avoid inoculation during accidental disease from travel or change of conditions, should be kept under observation for a few days. Tuberculin and other tests are unnecessary, as it is customary to kill the animals before the vaccine is used, and the autopsy furnishes more accurate information. Vaccination does not lessen the value of the animals for food.

The calves are cleaned as thoroughly as possible before they are taken to the operating room. They are then fastened to a suitable table and the abdomen is shaved and washed with soap and warm water. Antiseptics have been used, but are not necessary. In any case the final washing is done with large quantities of sterilized water and the skin dried with sterilized towels. The operators, in sterilized clothing, observe the usual rules of asepsis. A series of incisions is made in the prepared skin, about one inch apart. The area treated varies in different institutions, sometimes extending from the inguinal folds to the level of the navel, sometimes to the axillary folds. Other areas, such as the escutcheon or the scrotum, are sometimes inoculated. The sides and back are not used on account of the toughness of the skin. If more than slight bleeding occurs it is checked by pressure with sterilized towels. The "seed" vaccine is spread over the prepared surface and allowed to dry. The seed is of various kinds, either glycerinated bovine virus selected with care from particularly well-developed vesicles and of tested bacterial purity, selected humanized virus, or material derived more or less remotely from human variola. Some of the best strains in Europe are of this kind. It would be of great scientific interest and some practical value to have records of all vaccine strains, but as it is, makers often do not know or are unwilling to state the sources and nature of the seed.

The material is gathered between the fourth and sixth days, or at a time when the vesicles are well-developed but show no evidences of suppuration. At the proper time the animal is again put on the table, the abdomen thoroughly washed with warm water and soap, rubbed by hand, finally washed with sterilized water, and dried. This removes the dried superficial epidermal scales and does not break the vesicles. For the removal of the pulp a large curette is drawn along each row of vesicles, taking these off very thoroughly without much contamination with blood. After the pulp is all secured, it is ground in a special mill under aseptic precautions, in order to render it homogeneous. It is then thoroughly mixed with glycerin and kept for several weeks to "ripen."

The object of the glycerin is to destroy the bacteria, either in the vesicles at the time or accidentally introduced into the pulp.

Copeman proved that in glycerinated pulp the bacteria become gradually reduced in number, and even disappear at a time when the specific agent is still unimpaired. Drying has a similar effect on vaccine, but glycerin has the advantage that besides dehydrating the germs, it permits the formation of a homogeneous emulsion, part of which can easily be tested, and so permit accurate conclusions as to the qualities of a large amount of lymph. In glycerinated virus the specific action has been found present after as long a period as one year, but it may become inert within a month after the bacteria are killed, especially if the virus is exposed to ordinary summer heat. Great dilution does not destroy the practical efficiency of glycerinated lymph. The usual proportion is about one part of lymph by weight to ten parts 50 to 60 per cent. chemically pure glycerin, but dilutions of 1 to 2000 have given good results. One calf may furnish 3000 to 5000 portions, and perfect vaccination has been obtained from lymph representing one fifteen-thousandth of the yield. But this gives only the favorable aspect of the glycerin. Its effects on the bacteria and on the specific germs are modified by other factors. Glycerin acts best on bacteria at a temperature of 37° C. or above, very little at low temperatures; but the vaccine germs are injured by temperatures very little above 37° C., though they resist cold to a remakable agree. Moreover, the bactericidal action of the glycerin is very imperfect in practice, so that careful tests are necessary, even if the ripening has been carried out the usual time of four to six weeks.

Valuable as glycerin has been, it does not obviate the need of scrupulous cleanliness, and until we are able to cultivate the specific organisms pure, efforts should be made to find a better agent. Such efforts have in fact been made. Green (1903) showed that chloroform vapor eliminates the bacteria while leaving the specific elements fully potent. He reports 48,027 cases vaccinated with chloroform lymph, giving 97.6 per cent. of success, and an insertion-success of 91.3 per cent. As he points out, the method has especial value in sudden and urgent demands for lymph and in hot climates. Gaylord and Wheeler have shown that potassium cyanide in 1 to 200 normal solution has a complete bactericidal action without in any way injuring the specific organisms.

Glycerinated lymph is generally dispensed in small glass tubes, each containing enough for a single operation. In Europe it is also sold in small bottles, for vaccinating on a large scale. Ingenious modifications consist in putting up glass or ivory points, coated with the lymph, in sealed glass tubes. Since January 1, 1910, the sale of dry points has been prohibited in the United States. Under the Act of Congress of July 1, 1902, regulating the propagation and sale of virus, an improvement in purity and potency of vaccine preparations has come about.

The preparations are rarely free from bacteria. The extensive examinations of Rosenau and many others rarely show no growth, but the number may be very small. It seems quite possible to reduce it to less

than twenty per preparation. In "poor" vaccine there may be from several thousand to a number too large to count. Vaccine in all forms, dry or glycerinated, is capable of deterioration from a number of causes. Kept free from bacterial contamination and at a low temperature, the virus remains active for many months. High temperature is likely to weaken or even destroy the activity of the virus. Accordingly, lymph should always be kept in cool places, including the time of transportation, and should not be used at all if more than three months old.

The question of the relative strength of bovine and humanized virus is not a simple one, because there is no constant standard for either, and the proportion of takes with the two kinds varies greatly. Much humanized virus was almost or quite inert in the days when it was the only kind used. Bovine virus also may become weak. Weak virus seems attractive to some, but its use goes far to defeat the object of the operation and to give opponents of vaccination arguments against its value. The ideal should be the most intense specific action compatible with a safe local lesion.

The practical advantages of bovine virus are obvious. It permits selection and cultivation of seed more than does human vaccine. It can be prepared in large quantities, at short notice. It is free from the danger of syphilis, and with proper safeguards can be made as harmless, bacteriologically, as human virus can. The chief disadvantage is the possibility of contamination with pathogenic germs; but this can be wholly avoided by careful examination of material before it is put in the hands of vaccinators.

The Operation.—The first method, and that of Jenner himself, was simply an imitation of the variolous inoculation. Punctures or short incisions were made and the virus inserted. Later, blisters were raised on the skin and the virus placed on the abraded surface. The incisions were increased in number, then cross-scratches were made, and finally the operation became a denudation of the epidermis, sometimes of very considerable extent. The disadvantages and dangers of such an operation are obvious, for while it is possible to abrade so superficially that the vaccine will take and yet the epidermis heal over before the vesicle forms, as usually made the abrasion is followed at once by a scab of more or less thickness, under and around which the lesion must develop. The scab not only interferes with the development of the normal vesicle, but is irritating and induces rubbing or scratching, which promote secondary infection and give the most favorable conditions for the development of infections from germs either previously in the skin or introduced in or with the vaccine. Tetanus especially may be expected to flourish under just such conditions.

The best method would seem to be the simplest; and, in fact, incisions are the only operations permitted by the vaccine laws of Germany and are recommended by the Local Government Board of England. Many experiments have been made with the introduction of vaccine virus into the body in other ways, subcutaneously, intravenously, by the peritoneum and the alimentary canal. Immunity can be produced in all these ways, but is slower, less frequently successful, and requires larger

doses, 10 to 37 cc. per kilo. Sometimes there is marked hypersensibility to the subcutaneous method.

The point of election for vaccination is the outer surface of the upper arm, over the insertion of the deltoid muscle. This is not only convenient for the operator but also for the patient during the development of the lesion, and it seems less likely to be followed by severe glandular complications than are many other parts. The leg is sometimes vaccinated in order to avoid the disfiguring effect of a vaccine scar. In regard to this it should be said that a normal vaccine scar is not a deformity, and on the other hand any part of the leg is more exposed to traumatism and therefore to complications than is the upper arm. The writer always refuses to vaccinate on the leg unless the patient will stay in bed until the vesicle has healed, an objection that never fails to change the situation. If the leg must be vaccinated, the operation should not be done on the front of the thigh, but on the calf below the head of the fibula. Jeannerrets' suggestion, to vaccinate on the feet in young infants, has something in its favor.

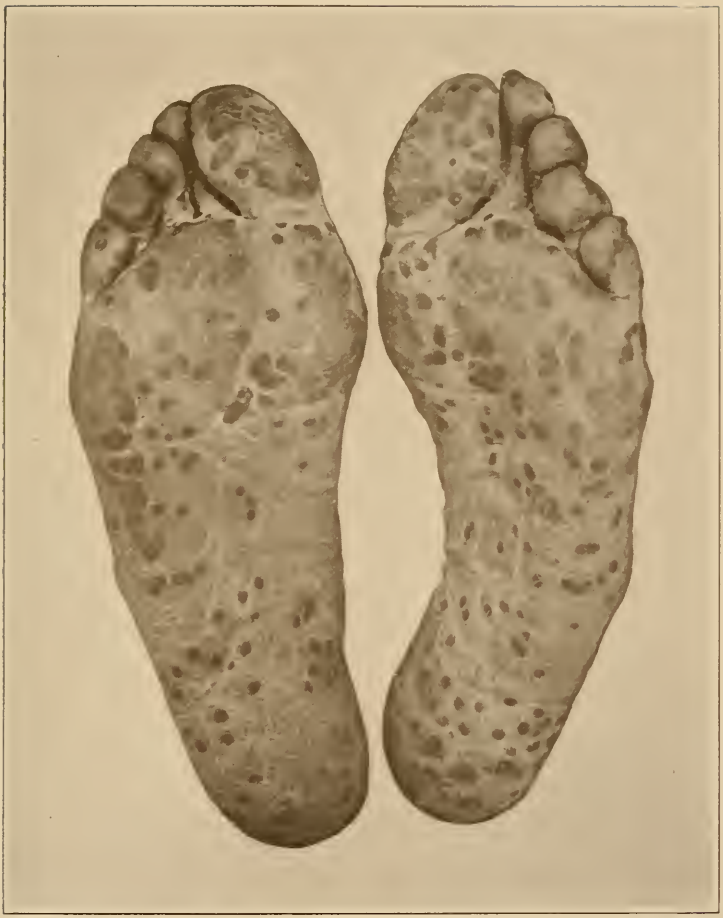
The number of insertions has an important bearing on the probability of taking, as well as on the protection, and we should not depend upon one. The German regulation of 1899 requires at least four incisions, each 1 centimeter long and 2 centimeters apart. The Local Government Board of England directs that four vesicles should be produced and that the total area of vesicle formation should be not less than half a square inch. The author's plan is to make not less than two incisions, each about one-half inch long, and from three-quarters to one inch apart; but in case of exposure to smallpox to make three or four, each one-half inch long.

"Vaccination is to be looked on as a surgical operation and carried out with all the precautions necessary for the prevention of septic infectious disease. Especially must the physician carefully consider the cleanliness of his hands, the instruments, and the place of operation" (German requirements of 1899). The seat of the operation must be clean, but not necessarily treated with antiseptics. Usually it is enough to clean the skin with sterilized water, but if the arm and the clothing are dirty the arm must be thoroughly washed with soap and water. Even in such cases it is doubtful whether antiseptics should be used, but if they are they should be washed off with alcohol and ether. The less the skin is irritated the less the danger of complications.

The best instrument to use is a scalpel, sterilized by dry heat, steam, or boiling. The "point" itself may be used, and is much more convenient since it requires no sterilization at the time, but it is usually dull, and makes a wider cut than does a scalpel. The incisions should not be deep enough to draw blood in large drops. Minute drops do no harm. If the incision is too deep it is better to make another. A little practice enables one to estimate the toughness of the skin and the sharpness of the blade, and to get at least the latter part of the incision the proper depth. (Cross-scratches and punctures are forbidden in Prussia.)

In the incisions the virus is gently rubbed, *not ground*, and then allowed to dry. Dressings are not necessary in the beginning. Pads, plasters, and shields increase irritation by heat and moisture and often cause

PLATE XXVII



Smallpox. Skin of the Soles of the Feet Cast off in One Piece and Showing Disks.

softening and breaking down. If the clothing is not perfectly clean it is well to pin a piece of sterilized calico on the sleeve so as to protect the seat of operation. Bathing need not be omitted, nor any ordinary occupation avoided. A properly made wound quickly heals. A normal vesicle has a tough skin and cannot easily be broken before it is mature. If the vesicles become broken a light protective dressing, not more than four thicknesses of aseptic gauze, should be put over the wound in such a way as not to rub. Collodion answers well, but should only be applied along the edges of the gauze. If the vesicles become infected they should be treated like other infected wounds, and by no means neglected from fear of ruining the vaccination. It is better to vaccinate a second time than to allow such a wound to go untreated.

Clinical Features of Vaccine in Man.—The best indices of the efficacy of vaccination are the course of the vesicle, the general symptoms, and the scar. Ultimately we may learn more exact guides to the immunizing power of vaccine, but at present we can only say that if the vesicle and scar are characteristic there is more or less immunity; if they are not characteristic, we must admit that immunity can not be considered present. The importance of knowing the characteristics of the vaccine lesions is therefore obvious. It is chiefly on account of the great diagnostic value of the vesicle and scar that subcutaneous methods of vaccination are not to be commended.

The typical features of vaccinia are singularly alike in successful cases. The stage of incubation lasts about three days. The seat of inoculation may heal at once, or show a local reaction, such as redness or failure of the incision to heal rapidly, depending partly on the condition of the subject, partly on the irritation produced at the operation. At the end of the third day small papules appear. They are rounded but soon become flattened with increasing size, round or oval in outline, of a bright red color, and feel hard but superficial. On the fourth day the summit becomes vesicular, and a central depression or umbilication rapidly develops. By this time the skin around the lesion is deep red and slightly swollen, and this areola or halo grows wider as the lesion becomes mature. By the end of the seventh day the vesicle has reached its full size. It is round or oval, flattened on top, the middle part umbilicated, and sometimes shows a small scab from the incision. The top is whitish, yellowish, bluish, or grayish, sometimes compared with pearl or alabaster. The sides are sloping; the skin close to the base is deep red, extending from 1 to 2 centimeters; and beyond this, sometimes, there is a paler zone which passes gradually or abruptly into the healthy skin. The contents of the vesicle are clear and watery but somewhat sticky. If punctured the vesicle may be shown to be multilocular. By the eighth day the vesicle looks yellowish; the middle part is sometimes fuller for a short time, but in a day or two sinks down, from desiccation ("secondary umbilication"). The areola is often redder at this time, 2 or 3 centimeters or more in radius; the surface is rough, like orange-peel; the edge is often sharply circumscribed. This part is indurated, sometimes quite deeply. Its outline may be very irregular, with islands of red skin near the edge. In such cases the arm is swollen, the skin feels

hot, the axillary glands are swollen and tender. From the ninth day the areola fades, sometimes becoming yellowish from altered blood; the swelling subsides. From the eleventh or twelfth days the vesicle rapidly dries, forming the "scab," which is brown, hard, and wrinkled or fissured. Finally, sometimes not until the end of the third or fourth week, the scab falls off, after becoming loose at the periphery. The scar at first is deep; the edges are sharply defined; the floor flat, and deep red in color. It slowly grows pale and nearer the level of the skin, and shows distinct pits or "foveations," one of the most important features of a "good" vaccination. The final size of the scar is much less than that of the recent state or the mature vesicle.

The local sensations associated with the development of the vesicle vary much in different individuals. Some do not complain and show no evidence of rubbing or scratching. Others, who do not seem more severely affected, complain bitterly, and can not be prevented from rubbing, scratching, or tearing at the skin. During the height of the development of the vesicle the patient often, but not always, experiences more or less malaise, loss of appetite, sometimes nausea or even vomiting, headache, and pain in muscles and bones or in the lumbar region.

As regards the body temperature Hennig and Bohn found a slight rise—0.5° to 0.7° F. in the first three days—but Sobotka could not. If present it is doubtless due to irritation of the wound. From the third to the seventh day the temperature is remittent, rising a few degrees, and remains about this point but with less marked remissions for two or three days longer, and then rapidly falls to normal. The fever does not seem to bear any proportion to the size and number of the lesions, provided they are not complicated, but is closely related to the areola, according to Bohn. Severe nervous symptoms, especially convulsions, do not occur. Huguenin looks upon fever as an essential part of vaccinia, as Zaehrer (1846) did long before. According to him children who do not have fever must be vaccinated again, but Sobotka in a few cases could find no definite elevation of temperature in the vaccinated newborn. Vaccination after a take does not alter the characteristic curve, nor does opening the vesicle (Sobotka). The nitrogen excretion is increased for a short time about the tenth day, and diminished later.

The red-blood corpuscles and hemoglobin show no distinct anomalies in vaccination, but the leukocytes, according to several observers, are increased. In primary vaccination Sobotka and Enriquez and Siccard found a leukocytosis of as much as 23,000, the former with the polynuclears, the latter with the mononuclear cells increased; myelocytes were rarely present. Billings found a maximum count of 15,000 leukocytes, with the neutrophiles especially concerned, most marked from the sixth to the eighth day, and disappearing in two to four days more. Sobotka also found an early leukopenia, and a secondary leukocytosis, beginning about the tenth day, with an intermediate low leukocyte count. Courmont and Montagnard saw nothing abnormal in the blood in adults, and Enriquez and Siccard found the blood negative in generalized vaccinia. Sobotka calls attention to the resemblance of the blood changes to those in variola.

PLATE XXVIII

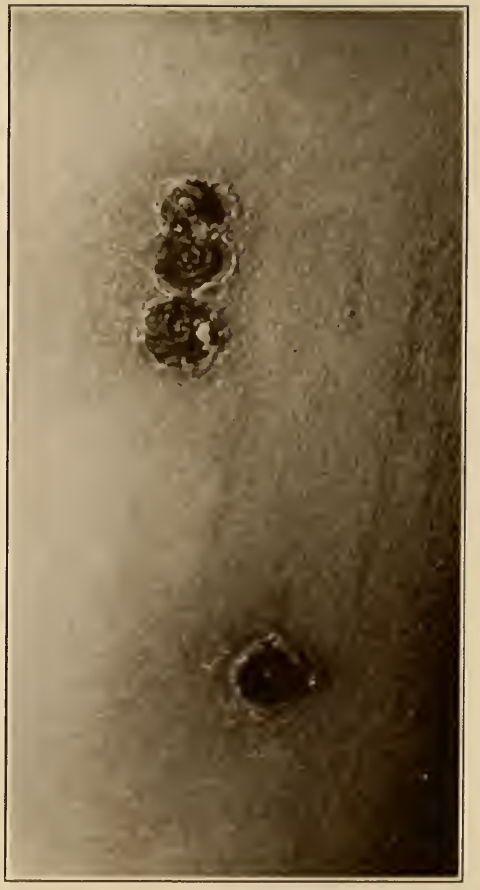
FIG. 1

Fifth Day.

FIG. 2

Seventh Day.

FIG. 3



Twelfth Day.

The Nature of the Changes in the Body after Vaccination.—Our knowledge of the processes brought about by vaccination is not as complete as it is in the case of several other infectious diseases. We can no longer look upon vaccination as merely a local skin lesion, but the difficulty of recognizing the parasites and the doubt surrounding inoculation experiments throw much uncertainty about the further details of the pathology. Investigations indicated, as pointed out by Huguenin, that it is not the dying out of the parasites that causes recovery from the symptoms, but that the body acquires a new condition, in which the infectious agent is indifferent; or, as it is now expressed, the body is immunized, and actively so. The immunizing process seems to take place in the skin and to remain especially there. Experiments regarding complement binding and complement deviation have been contradictory. The demonstration of precipitins has been equally uncertain, the results being obscured by the difficulty of getting clear fluids to work with.

That protective substances are formed in vaccinated animals is *a priori* probable, and was demonstrated as early as 1867 by Froelich. There are many apparent contradictions in the results, but the following summary gives the chief additions to our knowledge of the subject:

The blood-serum of vaccinated animals during the maturity of the vesicle or somewhat later—*i. e.*, from the eighth to the fifteenth day—is effective against subsequent vaccination. After that time the serum is not effective in checking wholly or in part the development of vesicles. This power is probably closely associated with a precipitating action.

The serum of immunized animals neutralizes vaccine, and evidently contains a substance that kills or inhibits the specific agent. The substance is produced in very small quantities, so that it can not easily be applied as a practical measure, and soon disappears from the blood, leaving the organism able to check the activity of the parasites and to render their toxins harmless. Under the influence of the parasite the body produces protective substances which are antiparasitic in other bodies. That the parasites are not killed at once, even under the active immunity, is demonstrated by many of the experiments. In the immune body the parasites are able to live for a time; in others, they can not only live, but also cause infection.

Freyer made clear what some earlier observations had shown to be probable, namely, that repeated injections of vaccine lymph furnish an antivirulent serum of greater power than can be obtained by the ordinary skin inoculation. At present this work has no practical application, but its theoretical bearing is very important, and modifications of the previous experiments may open up new therapeutic possibilities. Von Pirquet[1] has made an interesting contribution to vaccine pathology. According to him the areola is the result of the interaction of the lymph and specific antibodies.

Empirical Facts Regarding the Immunity of Vaccinia.—Vaccination produces immunity toward itself at a somewhat variable period. When

[1] *Klinische Studien über Vakzination und Vakzinale Allergie*, Leipzig u. Wien, 1907.

vaccination is repeated daily, as in the "vaccinization" sometimes used, it ceases to take usually between the fourth and sixth days. By the eighth day in a normal vaccination there is immunity not only to vaccination, but also to smallpox. Exceptions to this made Layet put the period of safety at the ninth day, and Burckhardt the eleventh. Most of the experience regarding the exact period of immunity against smallpox is derived from the early days, when the results were tested by variolation. Sacco got only local eruptions by inoculating smallpox from the eighth to the eleventh day; none at all after that.

It is irrational, however, to fix a definite time for the appearance of vaccine immunity. As in other diseases this varies within certain limits, according to the subject and the intensity of action of the vaccine.

A very important practical question is with reference to insusceptibility to vaccination, regarding which there has been much unnecessary difference of opinion. It was known in the period when smallpox was universally prevalent that certain people escaped it. The conditions can hardly be essentially different in vaccination. It is not to be supposed in either case that the immunity is permanent and complete. Illoway has published a case suggesting that one part of the body may be immune and others not, toward vaccination. If we admit, as some do, that there is no such thing as natural immunity against vaccination, we have to ascribe all the failures to imperfections in the lymph or technique and from a practical standpoint we cannot do better than take such ground. The alternative is scientifically well-founded, but can not be positively proved. Few can say, with Cory, that they have made many thousands of vaccinations without a failure, unless the criterion of success is placed dangerously low; but many can recall cases in which several unsuccessful attempts have been made, and then at some later time the patient has taken vaccination or acquired smallpox.

Smallpox itself does not render the body permanently immune to vaccination as is proved by numerous cases. It is often assumed that if vaccination takes, the subject would have taken smallpox if exposed; on the other hand, if it does not take the subject is supposed to be immune. Neither conclusion is justified, and the second one has often led to serious consequences.

Congenital or Hereditary Immunity.—Curiously in contrast with the disbelief in temporary insusceptibility to vaccination is the view that has been expressed as to inherited immunity from vaccination of the mothers. There are several sides to this question. In the first place it may be said that vaccination has not been general enough nor perfect enough to account for a large number of immune children. There are doubtless cases of congenital immunity to smallpox, from intra-uterine infection; but these are too rare to permit any other conclusions than that vaccination in the late stages of pregnancy may give immunity to the fetus. The most important aspect of the question is that no convincing investigations have been published demonstrating the alleged immunity on a large scale. As no evidence has been advanced showing the duration of immunity acquired in this way there is no reason to depend upon it in practice. Vaccine immunity can probably be acquired, as that of

variola is thought to be through milk; but very little is known on the subject, the scientific interest of which is great.

As vaccine immunity varies in the time of its appearance, so does it vary in duration when once established. This general law, true of all diseases that produce immunity, was often unrecognized in the early days of vaccination, and even now is often overlooked. Failure to recognize it lies at the basis of much of the present-day smallpox, and much of the antivaccination movement. Even in Jenner's time there were those who doubted life-long immunity, some of them putting the time as low as three years. Early cases of smallpox in vaccinated people and early vaccinations were misunderstood, and it was not until revaccination was carried out on a large scale that materials were prepared for such a demonstration as that of 1870–1871.

Since revaccination is an essential part of the operation it is necessary to learn something about its operation, and Bohn gives a useful classification of the results of this in practice:

1. Completely successful. Lesions precisely like those in primary vaccination; all the phenomena severe. Incubation three days, traumatic reaction; rapid formation of papules and vesicles; marked areola; typical pustule at the end of the seventh day. Fever on the fourth day; pain and swelling of the axillary glands on the sixth day; induration of the areola on the seventh and eighth days, with swelling of the upper arm; end of fever at the tenth or eleventh day, after going as high as 104° F. This form is seen especially when revaccination is done after a long interval.

2. Like the first class, but with a more rapid course. Height of the pustular stage on sixth day; fever from the fifth to the eighth day; slight glandular swelling.

Both of these classes furnish active lymph on the fifth and sixth days.

3. Short incubations, twenty-four to thirty hours; at the end of this an itching papule; vesicle on the fourth day, with or without umbilication; pain in the axilla. On the fifth day a brief appearance of areola, with very little fever. By the eighth day desiccation. From this and the forms to be described vaccination cannot be carried out.

4. Rapid development of an abortive lesion with minute vesicle on the second and third day; very small areola. This group cannot be sharply separated from—

5. In which there is either no reaction, or only a slight erythema.

These incomplete lesions have an important but still unsettled bearing on the completeness of immunity. They often result from and indicate imperfect immunity, and the partial success may be said to increase the immunity. But how long this is going to last in an individual patient we cannot tell. Such patients, in times of danger, should be revaccinated.

It is clear that no fixed period can be given for the duration of vaccine protection. The ten-year average is probably too long for the individual, but gives good results when followed on a large scale; the periods of three months or one year advocated by certain vaccinators is shorter than is necessary for practically complete protection; the seven to nine

year interval of Japan is a good one in many respects, though perhaps not better than the revaccination in the twelfth year obligatory in Germany. The success of revaccination varies much in different times and places, a large part of the variation being obviously due to perfection of technique and quality of lymph. In Germany it often exceeds 90 per cent., and in any place where the primary vaccination is good it is usually more than 50 per cent.

Vaccinated people may acquire smallpox, just as in some cases smallpox occurs a second or even a third time, but they do so in much smaller proportion than unvaccinated. This has been shown so often that it is remarkable that those who oppose vaccination because of its occasional failures do not recognize the fact. The general superiority of the revaccinated German soldiers over the civil population in 1870–71 has been mentioned. This becomes obvious by comparing some figures. The mortality in the army was 3.53 per 10,000; in Dresden, 32.66 per 10,000; in Berlin, 63.26 per 10,000; and in Hamburg 107.5 per 10,000. The total statistics for Germany are most convincing but a few examples must suffice. According to the reports of the Imperial Health Office there were among the 64,000,000 German population in the ten years, 1901–1910, only 380 deaths from smallpox. In Berlin there were 70 cases (not deaths) in seven years, in Cologne 1 in ten years, and in Frankfort 9 deaths in ten years. The cases are most frequently in foreigners, and the cities most affected are those chiefly resorted to by foreigners.

Another well-demonstrated fact is that vaccinated people who contract smallpox have it, on the average, much less severely than others. Huguenin, from the statistics of 62 hospitals, gives the following: Mortality of unvaccinated from smallpox 46.6 per cent., of vaccinated 9.2 per cent. These figures do not apply to other statistics, as both the type of epidemic and the efficacy of the vaccination vary. In St. Louis widespread vaccination of children has been opposed. The majority of children in the public schools are now vaccinated, but those in the private schools are not. Between April 1, 1901, and March 31, 1902, and April 1, 1904, to November, 1910, 195 cases of smallpox appeared among school-children; 45 of them had been or were in the public schools; of these 195 only 3 had been vaccinated, none within a recent period.[1]

Striking evidences of the protective value of vaccination have been seen in the Philippines, Cuba, and Porto Rico. In the former, during the Spanish rule, the mortality from smallpox was about 6000 per year. By 1906 over 3,000,000 of the population were vaccinated without a death from the operation, and no deaths from smallpox since the completion of the work. In one place out of a population of 2000, 1000 unvaccinated people took smallpox from an inoculated case and 400 died; 800 were vaccinated; there was no case of smallpox after the incubation stage and no deaths. The other 200 people fled.

Abnormalities of Vaccination.—Vaccination does not always run the typical course (even in primary cases) that has been described. Jenner

[1] *Interstate Medical Journal*, 1912, vol. xix, No. 2.

well understood this and pleaded for a careful training on the part of vaccinators; but this has often been neglected, with disastrous results in many cases. The variations are numerous, but can be placed under a few simple heads, as in the classification of Colcott Fox, modified by Pernet: 1. Local abnormalities or irregularities in the development of the vesicle. 2. Incidental exanthematic eruptions. 3. Diseases inoculated with lymph at the time of operation. 4. Diseases chiefly septic, which find a nidus in the wounds subsequent to the operation. 5. Diseases excited in subjects especially predisposed to the same. 6. Accidental vaccination. 7. Intercurrent disease.

The local lesion may be atypical either in its physical characteristics or in the time of its evolution. Differences in the time and duration of the various stages are common in revaccination, and have been described in connection with that. In primary vaccinia they are not so usual, but may occur either from partial immunity or from inferior lymph. Rapid beginning sometimes occurs, and is likely to be followed by an abortive later course. Poor lymph often causes slow development of the vesicle, which may not appear for from several days to several weeks, or even months, as claimed by some authors. Certain accidental causes have some bearing on the rate of development of vaccination. Cold retards it; warm weather often hastens it; existing diseases often delay it. A delay of more than three or four days should stamp the operation as imperfect, unless a typical lesion follows. In that case the event should be recorded. Sometimes if a second operation is done before the appearance of the papule, both inoculations develop simultaneously, or the one overtakes the other and they reach maturity at the same time.

This phenomenon, known since the early days of vaccination, has never been explained.

The anomalies of the local lesion may resemble those described as occurring under revaccination, but there are some others that are more certainly due to peculiarities of the lymph. They have long been known as "spurious" or "pseudovaccinia," "vaccinoid," vaccinella." These have so great a variety that it is difficult to classify them; but if we bear in mind the numerous transitions, the classification of Morrow is very helpful. He described:

"1. A vesicle containing opaque or straw-colored lymph, which makes its appearance usually on the second day; is irregular in form; the areola may be complete by the fourth, fifth, or sixth day. There is nothing fixed or definite in its course; it suppurates; dries up; the scab usually falls off by the tenth day, leaving a pigmented base.

"2. A small reddish tubercle, more sensible to the eye than the touch; enlarges to fourth or fifth day; crusts over; dries up and disappears, leaving no cicatrix.

"3. A single bulla, or instead a group of herpetic vesicles ('water pocks,' or 'vaccinæ bullosæ,' or 'pemphigoides'), containing transparent fluid, developed from a non-infiltrated base, with thin, tense walls which soon burst. The exuded fluid may give rise to eczematous or phlyctenular eruptions.

"4. A vesicle which may run a normal course until the eighth or ninth day, then rupture, crust over, with progressive ulceration beneath. The ulceration may extend both superficially and deep. There is usually pain and swelling of the axillary glands, and a high degree of constitutional disturbance.

"5. A pigmented tubercle supposed to be a specific product of bovine lymph, as its appearance dates from the introduction and general use of animal vaccination in this country; it is known as the 'raspberry sore.' It attains the dimensions of a large pea or coffee-grain; globular or irregular; of apple-jelly hue, or from a bright to a dusky red. It is soft and elastic, and gives a deceptive indication of fluid. Puncture is followed by the escape of a drop of reddish serum, the inoculation of which, according to some observers, produces a lesion of identical character. In from four to eight weeks it gradually disappears, leaving pigmentation but no cicatrix." As Morrow pointed out, this probably is not a new sore due to bovine lymph. It seems unnecessary to separate this from the second group, of which it seems to be an exaggerated example.

The explanation of these anomalies is impossible at present. They probably depend wholly upon imperfections or contaminations, or both, of the virus. There is no convincing reason for looking upon them as indicating protection against smallpox. The writer has seen several cases of smallpox in the last few years with histories and sometimes recent scars of these anomalous sores. Neither is there any reason to believe that these sores are related to vaccinia as varioloid is to smallpox. In some cases there is a short immunity to vaccinia, and sometimes (hard to prove) apparently to smallpox; but neither are constant. They are related to "vaccinia without eruption." This may be admitted as a theoretical possibility, but it has no practical value.

In all cases where the vaccine lesion is atypical in course or in the scar it leaves, the operation should be repeated within a period depending largely on the danger of smallpox. If that is present, it is better to vaccinate at once; if not, within six months or a year at most.

An interesting but unimportant anomaly is the appearance of small vesicles near the principal ones about the third or fourth day—secondary vesicles, or "vaccinolæ." The writer is convinced they are not always due to accidental inoculation of the surface of the skin, but that they arise from germs transported in the skin. They are not uncommon in vaccinated calves, and recall the distant eruption in natural or inoculated smallpox. They do not necessarily indicate a strong or active specific germ, but in calves often follow inferior lymph. Nobl explains them by delayed formation of antibodies.[1]

Incidental eruptions have been noted from the beginning of vaccination. They depend upon the same general causes as other similar skin manifestations, and require a certain bodily predisposition. They have various types—roseolar, resembling the rashes of measles or German measles, or more diffuse like that of scarlet fever; or they are urticarial or like the various manifestations of erythema multiforme. Most of them

[1] *Zeitschr. f. Kinderheilkunde*, 1912, orig., Band iv, p. 427.

begin near the seat of inoculation, but the erythematous form has a special predilection for the extremities, and the urticarial variety may involve the mucous membranes, as the bronchi. These two forms may begin as early as the second day; the more superficial eruptions usually late, from the seventh to the tenth. Minute vesicles sometimes occur at the height of the rash, and pigmentation with degeneration follows. Relapse of vaccinia has been reported by a few writers within a month or six weeks of the operation.

An anomaly of some importance is the hypertrophied scar that sometimes follows. It may occur even after a typical and uncomplicated lesion. Red at first, it finally becomes pale. It is rather hard, involves the true skin, resembles a keloid in appearance, but usually disappears very slowly, and thus is free from the most important characteristic of true keloid, which, however, sometimes occurs in the negro. In some cases a growth of hair is stimulated around the scar.

Generalized vaccinia is a term that has been applied to conditions not always the same. Strictly speaking it should be applied to cases in which a widespread eruption appears on the body, with the anatomical and infectious characters (inoculability) of the primary vesicle. Most of the cases reported under this name have been eczema or other skin disease in which vesicles or pustules have occurred in larger or smaller numbers. In some it could be demonstrated that multiple infection had occurred from scratching. In many the lesions were not characteristic in course, though they were in anatomical features. Henoch has emphasized the close anatomical resemblance of certain eczematous and accidental eruptions to vaccinia and variola. In a few cases there was a widespread infection without a previous skin disease. Martin reported one in which a calf was successfully inoculated from the contents of some of the vesicles, and from the calf in turn a number of children and an adult. Groth reports a case and states that from 1885 to 1900, out of 2,285,579 vaccinations in Bavaria there were 50 to 60 cases of generalized vaccination. As Malcolm Morris says, the remarkable thing about generalized vaccinia is that it is not more frequent. The prognosis is good in simple cases; bad in those depending upon an eczema.

Accidental vaccination and autovaccination are not very uncommon. They are likely to occur from scratching of the vesicle, though they have often been produced by infection from one person to another. In many cases the genitals have been the seat of the secondary vesicles, often producing, especially on the vulva, lesions that may give rise to much difficulty in diagnosis. The same difficulty often arises when the vesicle is in other parts of the body. Another common seat of accidental vaccination is the face. Mucous membranes in various localities have been involved. A common and very important locality is the eye, either in the conjunctiva or the cornea, and which was fatal in a case reported by Dietter. Blindness has often followed, and in 9 out of 61 cases there was more or less disturbance of vision.

Accidental vaccination of the nose is perhaps more frequent than the reports indicate. Lublinski gives 4 cases, 1 original. An interesting location was the tongue, in a mother who sucked the virus from her

child's arm. Physicians have inoculated their lips by blowing through vaccine tubes. The ease with which infection can take place is shown by a case in which a physician who dressed a child's arm infected the mother by a local examination. An important contribution to the subject is that of the zoölogist Blochmann,[1] whose own child was severely injured by vaccination.

The Complications of Vaccination.—The complications may be considered with reference to their mode of origin or to their anatomical or clinical peculiarities. Inasmuch as the same sort of lesion may arise either from infection with the vaccine or later, it is more convenient to follow an anatomical-clinical classification.

Vaccinal ulcers may resemble the anomalous ulcerating form previously described, but differ in that they may occur after the vesicle has made a typical beginning. They are especially likely to occur when poor virus is used, but may follow good vesicles which have become infected. Anemia and cachectic conditions are predisposing causes. The ulcers are indolent, with flabby and sometimes exuberant granulations. Glandular complications are not always present. Extensive loss of tissue may follow, with large and deformed scars. If the complication comes on after the vesicle has reached maturity some protection is probably given, but unless the operator is satisfied as to the course, the vaccination should be considered a failure. A number of deaths have followed this complication.

Postvaccinal gangrene can not be sharply separated from the preceding, but there is another form of gangrene, called *vaccinia gangrænosa* by Hutchinson, in which multiple eruptions occurred on the eighth day, surrounded by an areola, in which gangrene developed, with death in the second week. Such cases appear to be much less frequent now than formerly. It is probable that in some cases scurvy or some purpuric affection was present.

Hemorrhagic diathesis sometimes first shows itself after vaccination. There may be fatal hemorrhage from the incision. Similar hemorrhages have been observed after vaccination in leukemia. In all hemorrhagic cases the prognosis is serious.

The most important infectious complications of vaccinia are the *pyogenic diseases*, including *erysipelas*. These are much less frequent than when humanized lymph was used and when instruments were never cleaned. Erysipelas may occur at any stage of vaccination, and is spoken of as early or late, according to the period. It sometimes occurs so early that we must look upon the operation or the lymph as the exciting cause. In most cases it occurs in the second week. The areola is evidently an erysipelatous lesion, but its relationship has not been sufficiently worked out. In most cases there is a distinct history of rubbing or scratching and obvious uncleanliness. The disease has occurred in epidemics, due to some fault in lymph or operation, at other times with epidemic erysipelas of other parts of the body. The latter possibility is ground for an important objection to hurried vaccination during epidemics, which

[1] "Ist die Schutzpockenimpfung mit allen notwendigen Kautelen umgeben?" *Tübingen*, 1904.

often occur at a season favorable for erysipelas, instead of formal vaccination at a more favorable time of year.

The local and general phenomena are those common to erysipelas in any part of the body. The prognosis depends upon the condition of the patient, and the severity and extent of the erysipelas. Unless the complication comes on very late the vaccine vesicle is checked in its development and immunity is not produced. In any case the lesion is infected, ulcerates, and an atypical scar is the result.

Abscess, furuncles, lymphangitis, cellulitis, and *phlebitis,* suppuration of axillary glands, and *pyemia* are rare, but serious complications that need no special description. *Suppurative parotitis* is a rare occurrence after vaccination. In all the pyogenic complications it is important to treat the conditions according to the general and special rules that apply to such diseases in any part of the body, and never to neglect or even temporize with them in the belief that the vaccination may suffer. This must be considered a failure in all cases in which the vaccine lesion is involved early, or where its course is altered.

An interesting and important complication is *contagious impetigo,* which sometimes occurs in recently vaccinated people as it does in others. "When due to the vaccine, the cases develop in groups. The vaccine vesicles become pustular, itch severely, rupture early, and infect the body in many places." Voigt mentions a small epidemic following arm-to-arm vaccination from a healthy child, on the eighth day. In many cases the infection is accidental. *Pemphigus* is a much rarer complication, sometimes difficult to distinguish from impetigo. Erythema multiforme, E. iris, and other varieties to E. bullosum, occur in rare cases several weeks after vaccination, with the scab, sometimes obviously infected, still present. In these, as in all cases of anomaly of the lesion with accidental infection, early antiseptic treatment should be used.

Eczema, psoriasis, and various other chronic skin diseases, sometimes follow vaccination, especially when the operation is done in hot weather. In the majority the skin diseases are already present, not noticed or not brought to the attention of the physician, and then any increase in severity is ascribed to the operation. In all vaccinating the physician should ascertain the existence of a skin disease, and either not vaccinate at all, or, in case of danger of smallpox, try to vaccinate in sound skin. In such cases a light but efficient bandage may be used.

Herpes circinatus is a rare occurrence after vaccination, explained by infection with *Trichophyton tonsurans,* a common parasite of cattle.

Measles, scarlet fever, and other acute exanthemata sometimes occur in the course of vaccinia without causing any serious effect on each other. Jenner noticed that both measles and scarlet fever caused a suppression of the areola, which reappeared after the other exanthem faded.

Simultaneous Vaccinia and Variola.—It was early observed that smallpox and vaccinia could exist at the same time in the body, and though some assert that in such cases the variola is modified, others say, and more accurately, that the severity of the smallpox depends partly on the period at which the vaccinia is introduced. Considering the close relationship of the two diseases, it is easy to understand that they

can develop together, and that the immunity of one will check the growth of the other. The situation is not unlike that which exists when vaccine is inoculated on successive days. All the lesions may develop together until immunity is set up by the earliest, and then all subside.

Huguenin describes the chief possibilities with smallpox as follows:

1. In case vaccine is inoculated just before or during the primary fever of smallpox the latter proceeds uninfluenced, unless there has been a previous vaccination. The vaccine, however, fails because of the immunization of the body by the variola.

2. If the vaccination is made at the end of the stage of incubation of variola, both infections may go on side by side.

3. If the vaccination is made in the middle of the incubation of variola, the eruption of the former will occur two or three days before the primary fever of the variola. Only a mild smallpox or a varioloid develops.

4. If the vaccination is made in the beginning of the incubation stage of variola, the difference being six to eight days, the variola will be abortive.

5. In the first day of the incubation, vaccination prevents the smallpox, though there may be fever.

6. If a child in an infected house is vaccinated before it is infected, there will be no symptoms of smallpox.

There are, however, some exceptions. The variola may proceed unaffected by vaccination, which may not develop until after the smallpox has run its course. Vaccination and smallpox may occur simultaneously, the latter retarded but not rendered abortive. Or the vaccination may develop imperfectly and the variola run its course and even reach a fatal end. In view of the great number of more favorable cases, such accidents should not prevent vaccination in every case where infection is threatened. In the first three days after infection, even in the fourth or fifth, careful vaccination should be made in at least four places. In such cases, too, especially if the type of variola is severe, one may with advantage practise successive vaccination every day until the eruption becomes vesicular.

Syphilis is not to be considered as a possible complication if bovine lymph is used, except from extraordinary carelessness on the part of the operator or the patient.[1] The same may be said of *leprosy*, which has in rare instances followed arm-to-arm vaccination in leprous regions. Leprosy bacilli have been found in the lymph of vaccine vesicles in lepers (Arning and others). *Tuberculosis* also has only historic interest in connection with vaccine, though it will always be important for propagators of vaccine. Vaccination sometimes seems to accelerate the course of tuberculosis.

Tetanus has a remarkable history in connection with vaccination. It is so rare in general that only 7 cases could be found in the Index Catalogue, and McFarland could find only 15 altogether in the literature up to 1899; yet he was able to collect 52 cases reported more or less completely, and to learn of 28 more not well authenticated, after that

[1] Nobl (1907) showed that vaccine lesions in actively syphilitic cases do not contain spirochetes.

date. Since then a few more cases have been reported. McFarland found from a careful study that: (1) Tetanus is not a frequent complication of vaccination. (2) The cases occur in small numbers after the use of various viruses. (3) An overwhelming proportion occurred after the use of a particular virus. (4) Tetanus bacilli may be present in virus in small numbers, derived from manure and hay. (5) Through carelessness or accident the number may be greater than usual. (6) Avoidance of the complication is to be sought in greater care in the preparation of the virus.

Reading the accounts of separate cases, and still more those of epidemics of complications, gives one an unfavorable view of vaccination. Three things must be considered in this connection. We no longer, thanks to vaccination, see or suffer the horrors of pre-Jennerian smallpox with its complications. Nothing else would have removed these so effectually as has vaccination. In the second place, many of the accidents —almost all of the severe ones—are avoidable. Moreover, we need to take a broad survey of vaccination in order to get the real proportions. This has been admirably done for us by Voigt, for thirty years director of the Hamburg Vaccine Institute, having probably the largest vaccine territory in existence. In this time 400,000 persons were vaccinated in the institute; in the whole district, nearly 600,000 in twenty years. Out of 589,586 school-children vaccinated and revaccinated there were: Inflammatory complications, probably chiefly due to staphylococci, 35; 2 fatal. Erysipelas, 13; 2 fatal. Phlegmon, 4; 2 fatal. None of the pyogenic cases were due to the operation itself. Eczema, 293, 85 of which began before the vaccination. Urticaria, 32 cases. Impetigo, 85 cases, 50 of which were not due to vaccination. Tetanus, 1 case, recovered; this began on the fourth day, several days after the patient had fallen upon his head.

Another useful series of data is the following:[1] In Germany in thirteen years, 1885–97, 32,166,619 children were vaccinated; 115 of them died within a few weeks or months after the operation, from injuries presumably due thereto. This gives a mortality of 3.5 per million. In 67 cases only, however, was it probable the injuries were due to vaccination. In 1902 there were no deaths traceable to vaccination, but 2 from subsequent invasions. As the report says, *compulsory school attendance is far more dangerous than compulsory vaccination.*

At various times vaccination has been thought to have a curative effect upon other diseases. Most of them are diseases in which it would be difficult to prove the exact relations, such as whooping cough, leprosy (Rake), tuberculosis (Winogradoff), and various skin diseases. Hypertrophic scars, such as sometimes follow vaccination and nevi, seem more promising. In such cases superficial scarification and vaccination with lymph of good quality would seem justifiable.

The Practical Application of Vaccination.—There is a remarkable discrepancy between our knowledge of vaccination and its benefits, and the practical application of this knowledge for the prevention of

[1] *British Medical Journal*, April 16, 1904, p. 903.

smallpox. Errors of technique and exaggerated ideas of vaccine immunity have been partly responsible for the neglect of and opposition to vaccination; but, though we still need further information concerning many details, we have enough to warrant a much wider use of vaccine than now exists in many countries. It is certain that vaccination applied to the fullest extent, and repeated once or twice in the age of greatest predisposition, has almost abolished smallpox whenever it has been tried. Nothing else has done this, and the experience of every locality that has tried to get along without vaccination, depending upon sanitation alone, shows that until our ideas of smallpox are radically changed we are not likely to get a satisfactory substitute for vaccination.[1]

The continued existence of smallpox, often in epidemic form, makes more obvious the need of improvement; for, even when the disease is mild it causes far more deaths, more alarm, and more suffering than vaccination ever has, and, moreover, there is no reason to think that the type will remain permanently mild.

It seems expedient to consider some of the reasons for imperfect vaccination and the possible means of improving the condition.

1. There is no order, system, or uniformity about the operation. The result of this is that large numbers of people of all ages remain unvaccinated, usually because they know no better. This furnishes so large a proportion of predisposed subjects that smallpox once introduced is sure to obtain a foothold, and in the epidemics that result even some vaccinated people get the disease and some of them die. The proportion of unprotected people varies in different parts. Perhaps the conditions in Michigan are no worse than the average, as the excellence of its Board of Health has long been recognized. Yet among several thousand people examined by the writer within ten years with reference to this point, all above the age of childhood, only 60 per cent. had been vaccinated at all, and most of these had unsatisfactory scars. The limitation of a single vaccination and even of revaccination on the one hand, the great danger of smallpox on the other, and the advantages of widespread vaccination, make the subject not one of individual complaisance, but one that should come under the sanitary control of the authorities.

2. Systematic revaccination, an essential part of the process, is even more neglected. Carried out as it should be, it would make still more certain the protective influence of vaccinia, and so lessen the number of possible foci of variola.

3. No sufficient provision is made for the production of safe and trustworthy vaccine virus. Past experience has shown that the private manufacture of vaccine opens the way for a greater degree of carelessness than should be permitted in such an industry. Recently an inspection of establishments for the production of vaccines and analogous preparations has been made under a United States law. The establishments are inspected and the methods of manufacture, construction, and admin-

[1] Dock, Smallpox Quarantine and its Failure in Practice, *Journal of the Missouri State Medical Association*, January, 1912. An account of an epidemic in which a militia company was used, without success, to keep smallpox inside an asylum.

istration investigated. Samples of vaccine are examined, and, if there is any reason, the yearly license is revoked or suspended. The value as well as the need of such inspection is best shown by the fact that within a year of the beginning of the work, four establishments were refused licenses, and others were obliged to improve their methods, rebuild laboratories and barns, etc. There was also improvement as regards bacterial contamination of vaccine.

Unfortunately, the tests as to the specific activity of the virus are so far insufficient, and much of the vaccine used is seriously weak. Regular vaccination at fixed periods would add much to the certainty of securing good vaccine, because makers could prepare for the demand, and the virus would not suffer, as it does now, from insufficient ripening or from being kept too long after it is ripe.

4. There is no way of being certain the operation will be well done and the result accurately recorded. In many places local or State laws provide for compulsory vaccination, but this can be and is evaded in many ways. "Internal" and other fraudulent methods are practised, and false certificates are given by legally qualified but unprincipled practitioners who object to vaccination. Mothers suck out the virus as soon as the operation is done, and as no inspection of the result is necessary, unfounded security is set up, based upon a fallacious belief of widespread vaccination, inevitably leading to disappointment and to erroneous ideas of the value of vaccination.

For the best results to follow laws compelling vaccination it is necessary to have the active as well as the passive consent of the people, and it is sometimes said that Americans in general would never submit to compulsory vaccination. The writer thinks this is a serious error, and that the chief difficulty at present is the ignorance of the public as to the desired methods—an ignorance not entirely unconnected with defective laws and still more defective administration. The patience with which, in various parts of the country, the public submits to quarantine, detention, spasmodic and inconclusive vaccination, not to mention the unpunished malpractice of ignorant vaccinators, is the best argument in favor of the view that the population, as a whole, would welcome any wise and conservative law, based upon such experiences as those of Germany. It is sometimes said that general vaccination would open the way for a series of preventive inoculations for various other infectious diseases, but this is not necessarily so. Whenever it can be shown that any other disease can be protected against as well as smallpox can be by vaccination, and with as little risk, it would obviously be well to take advantage of the discovery.

Before any radical change can be made in our vaccination laws, physicians can do much to bring a better sentiment than exists at present, and also to improve the practice of vaccination. They should encourage vaccination and revaccination in all persons with whom they have professional relations, and do this not at times of epidemics, but as early as the occasion permits. They should advise and select a time when the discomfort of the operation and the danger of complications is least; that is, in the early summer or early winter, and when there are no

epidemics of dangerous contagious diseases, like scarlet fever, measles, diphtheria, croup, whooping cough, or erysipelas.

Parents should be advised to have children vaccinated between the ages of six months and two years, or earlier in case of danger. Children should also be revaccinated when they begin school, especially the public schools, with the danger from the carelessness of other parents. After that revaccination should be practised according to local conditions, without a longer interval than ten years until adult age is reached, and particularly when new occupations offer renewed dangers. So, for example, recruits, operatives in manufacturing establishments, and those who work in large stores or offices, should be revaccinated. Mail clerks and all employees on railroad trains should be thoroughly revaccinated.

Individuals with serious organic or constitutional diseases, with severe skin diseases, especially those that induce scratching, should not be vaccinated unless there is immediate danger, but the reasons and risks should be clearly stated to the patients, parents, or guardians, so that greater precautions may be taken. Revaccination in older people should not be done during the existence of any serious disease, unless there is distinct danger of smallpox. In such cases it should be practised, and the wounds carefully observed. During menstruation, especially the early part of the period, is not a good time for vaccination. The writer has seen vaccination and revaccination carried out several times in the last few years on most of the patients in a general hospital, and though some painful swellings occurred, there was no serious damage.

Every effort should be made to obtain good material. The operation should be looked upon as an important one, and sufficient time and pains taken to make it as aseptic as possible. The patient should be told of the necessity of noting the result and of treating any untoward symptoms, the accidental nature of which should be made clear. Records should be kept, as well for the information of the patient as for that of the physician. With the greatest care, however, certain risks are present, and so it is unwise for the physician to force the operation upon those who are unwilling, or to give assurances of absolute harmlessness.

CHAPTER XXIV

CHICKENPOX

By WILLIAM T. COUNCILMAN, M.D.

REVISED BY

E. J. G. BEARDSLEY, M.D.

Chickenpox (Latin, Varicella; French, Varicelle; German, Wasserpocken or Windblättern; Italian, Varicella or Morviglione) is an acute infectious disease occurring chiefly in children, characterized by a slight fever, mild constitutional symptoms, and an eruption which, if seen from the beginning, is successively macular, papular, and vesicular. The maculopapular stage is seldom seen, as it lasts but a few hours. The vesicles soon fill with clear contents and dry and shrivel in three or four days, leaving a granular scab. The disease is the mildest of all the infections, and without complications is attended by no mortality unless it attacks a child whose resistance has been exhausted by some other disease.

Etiology.—This is unknown and there is doubt concerning the essential seat of the disease. There is much evidence to show that the virus is not contained in the vesicles, rapidly dies out, or is not in an inoculable form. The disease is easily communicated, but the mode of infection is unknown. The weight of evidence is certainly against transmission by inoculation of the vesicle contents. Bryce, Heim, Vetter, Thomas and others were unable to produce the disease by inoculation. On the other hand, Steiner reports a successful inoculation in two cases which he cites in detail. While chickenpox is chiefly a disease of childhood, no age is exempt. The exemption of adults is probably in great part due to immunity derived from an attack in childhood. The epidemic studied by Tyzzer in the Philippines occurred entirely among adults. Welch and Schamberg have reported forty cases in adults, in the majority the mistaken diagnosis of smallpox having been made. While chickenpox prevails more at certain times, it is rarely present to so great a degree as to warrant regarding it as an epidemic. In large cities it is constantly present. When it appears in a family it usually affects all the children who have not previously been infected. It passes through institutions for children in the same way.

Pathology.—The anatomy of the skin lesions was studied by Tyzzer on vesicles excised at various stages. The earliest lesions in the epidermis are found in the areas of erythema which precede the formation of the vesicles. The first change consists in swelling of the cytoplasm and nuclei of the cells. The areas affected are often very minute, not more than two or three cells being involved. The cells undergo changes which have been described by Unna as ballooning degeneration. The nucleus of

a large swollen cell divides by direct division, and this process is rapidly repeated until a large number of nuclei are produced within the cell. The cells often attain enormous proportions. The nuclei are usually grouped in the centre, often so closely packed together that the apposing surfaces are flattened against each other. Exudation from the vesicles beneath the epidermis rapidly takes place and the fluid finds its way into the degenerated epithelium and separates the degenerating cells, forming spaces filled with fluid. The lesion may form from one or several centres, but the various small chambers quickly break into one another, forming a single vesicle. The degenerated epithelial cells do not form the rigid septa which are found in the smallpox vesicle. Cells in various stages of degeneration are found free in the vesicle contents or along its floor. The base of the vesicle in which there is an active exudation is almost invariably concave. The vesicles are usually unilocular and not umbilicated, although in the latter stages there is a tendency for slight depression of the top of the drying vesicle. The fluid within the vesicle contains fibrin, and coagulates spontaneously when removed.

The vesicles usually rupture very easily. Few polynuclear leukocytes are found, either in the corium or in the vesicle, unless infection by bacteria has occurred. Abortive cases without complete vesicle formation may occur. In these there is a marked localized degeneration of the epithelial cells without any appreciable exudation. These lesions, appearing as reddened, slightly elevated spots, show microscopically a portion of the epidermis wholly necrotic, with the cells disassociated and hyaline in appearance like those in the advanced vesicle.

There are no records of autopsies in uncomplicated chickenpox, so that nothing is known as to the presence or character of internal lesions. It is usual for chickenpox to leave slight cicatrices, which are quite characteristic in appearance. They are more frequently seen on the forehead, chest, and back than elsewhere. They produce little deformity, and are usually visible only on close examination. They are but slightly depressed, a trifle paler than the surrounding skin, and vary in size up to 4 mm. They are due to a very superficial destruction of the corium, involving only the papillæ. The destruction is never so deep as to involve sweat glands or hair follicles, hence the cicatrix is seldom foveated. Rarely there are more extensive cicatrices, usually the result of infection of the vesicles, with resultant small ulcers.

Incubation.—The incubation period may be from eleven to twenty-one days, but most commonly the symptoms appear on the thirteenth, fourteenth, fifteenth, or sixteenth day. Steiner, who is credited with having produced the disease by inoculation, found the incubation period in each case to be eight days. As a rule the incubation period is free from symptoms, although occasionally there is noted loss of appetite and general indisposition in susceptible children.

Symptoms.—The character of the onset varies. The appearance of the eruption is usually the first evidence of the disease, especially in children, but in some cases there are slight and occasionally severe febrile symptoms, with nausea and vomiting. Headache, a feeling of chilliness and general discomfort, followed by high temperature, are

PLATE XXIX

Eruption of Chickenpox. The Relative Frequency of the Pocks on the Face and Body is Shown.

not infrequently observed, especially in adults, and in such cases smallpox is often suspected. Rarely the initial symptoms in a child may be a convulsion accompanied by a sharp rise in temperature which disappears, as a rule, with the appearance of the rash. In young children delirium is not infrequently seen. Generally the initial temperature is low, not more than 101° F., less frequently greater degrees of temperature occur, and in such instances there may be marked nervous and mental symptoms. The temperature usually drops to normal with the appearance of the rash, but if the eruption is very abundant the fever may reappear and persist for several days. Children are usually restless and irritable on account of the itching of the vesicles, which is made worse by the scratching and rubbing which are almost impossible to prevent. Painful micturition may be cause by the presence of vesicles on the prepuce or urethra, or on the labia in females. The severity and duration of the symptoms depend on the number of crops and the abundance of each crop of vesicles. The lesions which show a tendency to severe inflammation, ulceration, or necrosis after rupture determine the severity and length of the illness. In the majority of instances there is little tendency to serious inflammation and the skin heals in a short time. In certain cases, on the other hand, there is a tendency to swelling and tenderness of the skin, and the formation of impetiginous crusts about the ruptured vesicles. There may be secondary infections due to scratching and widespread suppuration under the crusts, which may even result in necrosis of the skin and tissues. In these severe infections it is not unusual for septic erythematous rashes to occur as in smallpox. Scarlatiniform rashes are most commonly noted, and purpuric eruptions have been reported infrequently.

Prodromal Rashes.—These are by no means uncommon, although less frequently observed than in smallpox. They occur from two to twenty-four hours before the true varicellous eruption. The scarlatiniform initial rash is the most common, although morbilliform eruptions have given difficulty in diagnosis from measles. Initial urticarial rashes have been observed. These rashes may or may not be accompanied by fever, and if there is fever with a generalized flush or punctate rash it is often difficult for several hours to exclude scarlet fever. The initial rash usually disappears with the onset of the true varicellous eruption but less commonly persists for a day or more after the vesicles appear.

The Eruption.—When this is carefully watched from the beginning in many instances, if not in all, there is a macular and papular stage which precedes the better recognized vesicular stage. The macule persists but a short time, rapidly changing into a minute papule which resembles the rose spot of typhoid fever. The papule is slightly raised and often shows considerable resistance but does not usually have the characteristic "shotty" feel of the papule of smallpox. The vesicles appear in the central portion of the maculopapules and rapidly attain their full development, the time varying from three to thirty-six hours. They are transparent, oval or round, shining vesicles with sharp edges, which readily collapse if pricked and the contents pressed out. The vesicle is often surrounded by a slight, sometimes a marked, red or pinkish areola,

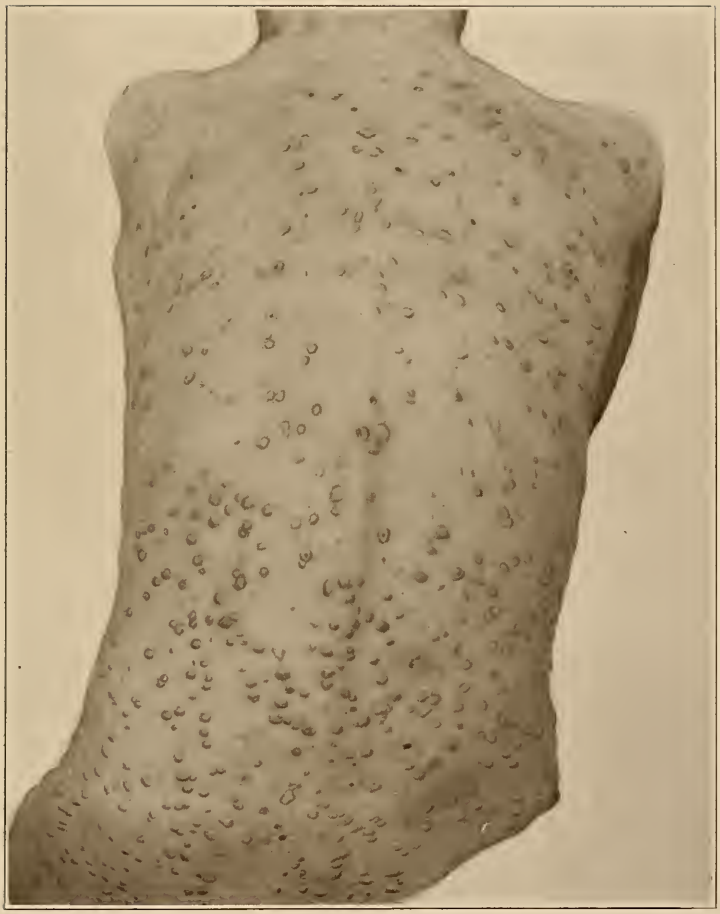
the remains of the macule, which gives the lesion the appearance of a large drop of water or glycerin upon the skin surrounded by a faint red line. Gregory compared the vesicular eruption to that which would appear if the skin were sprayed with boiling water. The erythematous ring usually fades before the vesicle matures and may be absent from the beginning. The characteristic vesicle is from 2 to 4 mm. in diameter, projecting 1 to 4 mm. above the surface and is not usually depressed in the centre; occasionally a few vesicles are found late in the disease with slight or even marked central depressions. The contents of the vesicle are clear, and it appears transparent beneath the thin covering. Before disappearing, the vesicular contents become more opaque but do not often become distinctly purulent.

The eruption generally appears first upon the chest and back, and, contrary to the eruption of smallpox, the body is more affected than the face and extremities. William Welch points out that the eruption of chickenpox appears, as a rule, on the covered body surfaces, while smallpox appears chiefly on the surfaces exposed to light. On the scalp, forehead, and extremities the lesions may be deeply set in the skin and give a resistant feel which may resemble the "shotty" feel of the papules of smallpox. Vesicles are rare upon the palms and soles, although they appear rarely in these areas. Lesions on the buccal mucous membrane and palate appear, but the vesicles are quickly ruptured and the lesions usually present the form of slight erosions. Vesicles also appear in the vestibule of the vagina and upon the prepuce, and may cause considerable swelling and irritation. The general duration of the vesicles is three days. They appear in successive crops, and the duration of the disease may extend into a week or longer. The vesicles may disappear by absorption, in which case there will be a very slight scaly crust formed of the dried epidermis, which is cast off and renewed. They are more frequently ruptured and a somewhat thicker crust results due to the presence of the dried exudation and deeper necrosis of the epithelium. The crusts are often dark in color and may be made up largely of coagulated blood due to injury by rubbing or scratching. The crusts lie, as a rule, more superficially than those of smallpox, but if the base of the vesicle has been infected the crusts may be set deep in the skin and leave disfiguring scars on healing.

Hemorrhagic chickenpox is fortunately rare, although it is not uncommon to have a minute hemorrhage into a few of the vesicles during the course. In the severe hemorrhagic forms large and small ecchymoses appear under the skin with smaller hemorrhages into the vesicles. This condition is sometimes fatal.

Complications.—In the usual case there is little to be feared from complications, as the majority of patients are but slightly ill and soon recover. There is a possibility of certain complications. *Gangrene of the skin* is rare. Hutchison has referred to it as "varicella gangrænosa," and Crocker wrote an excellent description of the condition. It occurs after the rupture of the vesicles and is apparently caused by secondary infection usually in children living in unhygienic surroundings, especially if the general health is poor. *Impetigo varicellosa:* Welch and Schamberg

PLATE XXX



Eruption of Chickenpox.

called attention to frequent infection of the chickenpox vesicles by impetigo and have termed the resulting occurring lesions "impetigo varicellosa." *Boils* and *abscesses:* Although far less frequent than in smallpox, boils and abscesses may occur during convalescence and especially on the scalp. *Erysipelas:* It is strange that erysipelas is not more frequent, but few cases of this complication have been described. Holt has reported three fatal cases. *Parotitis* has been reported very rarely. The reviser reported such an instance in 1909. *Thyroiditis* is an equally rare complication, but Allaria has reported an instance in which the gland suppurated. *Otitis media* occasionally occurs during an attack of chickenpox. Moy reported 17 instances in an epidemic of 875 cases. Mastoiditis, meningitis, and abscess of the brain may result. *Laryngitis:* Marfan and Halle reported two instances; in one it was necessary to perform tracheotomy, the child making a good recovery, but the second resulted fatally and the autopsy showed a small ulcer on the posterior surface of one cord, probably the result of a varicellous lesion. *Bronchitis and bronchopneumonia,* although unusual, occasionally occur in debilitated children. *Synovitis* and *arthritis:* Landon and Parret have reported instances of this complication. Semtschenke saw two cases with suppurative joints during an attack of the disease and Hoyges reports a similar instance in which several joints were involved. Several cases have been reported, in some of which suppuration occurred. Instances of *periostitis* have been noted.

Encephalitis, meningitis, paraplegia, monoplegias, and other nervous disorders have been reported as complications. It is difficult in these and in other rare complications, to decide whether the condition is a coincidence or occurs because of the attack of chickenpox.

Albuminuria and Nephritis. When nephritis appears during the disease it is one of the most dangerous complications. Henoch was the first to call attention to nephritis following chickenpox and reported four cases. Although albuminuria and nephritis are thought to be rare complications of chickenpox, the reviser feels sure that if the urine was systematically and carefully examined, both during the attack and subsequently, we would learn that nephritis as a result of chickenpox is by no means infrequent.

Diagnosis.—Chickenpox must be differentiated from smallpox, impetigo contagiosa, dermatitis herpetiformis, pemphigus, vesicular and pustular syphilitic eruptions, molluscum contagiosum, acne and herpes. The mose important differential diagnosis is from smallpox and this is discussed in the article on that disease. The differential points are as follows: (1) The vaccinal condition of the patient. Successfully vaccinated patients, especially if the vaccination is of recent origin, are extremely unlikely to have smallpox. (2) The eruption of smallpox is almost invariably preceded by two or three days' illness with characteristic symptoms. This is almost unknown in chickenpox in children, but it occasionally occurs when the disease affects adults. (3) The constitutional symptoms are much less marked in the usual case of chickenpox but with a severe attack of chickenpox an adult may be quite ill. (4) The distribution of the lesions in the two diseases is quite different. In small-

pox the uncovered portions of the body, namely, the face and distal parts of the extremities, show the greater number of lesions, while in chickenpox the trunk, especially the back, is most affected. The lesions of chickenpox appear sometimes on the soles and palms but never in such number as in smallpox. (5) The eruption of chickenpox appears in crops on successive or alternate days and the lesions are in all stages of development, while in smallpox the lesions show uniform development. (6) The histology of the skin lesions is different, chickenpox showing the formation of epithelial giant cells which are absent in smallpox; the chickenpox vesicle has a single chamber while that of smallpox is multiple. The epithelial cells in smallpox contain the cytoryctes, which are absent in chickenpox. Even the microscopic examination of the contents of the vesicle at the bedside may be decisive, for the presence of the large multinucleated epithelial cells speaks strongly for chickenpox.

From *impetigo contagiosa* it is sometimes difficult to distinguish chickenpox. A history of direct exposure to either disease will aid. The lesions of impetigo are chiefly on the face and hands, but in some cases the lesions may appear over all the body. The fact of the lesions of chickenpox occurring in crops is of value. The finding of a typical varicellous lesion in the roof of the mouth assists, as impetigo does not affect the mucous membranes. The lesions of *dermatitis herpetiformis* may be very similar to those of chickenpox, although it is unusual to find typical oval forms. The skin disease shows a marked tendency to recur, and a history of a previous attack is helpful in the diagnosis. In the early stage of *pemphigus* when small bullæ are present the lesions may be mistaken for chickenpox, but when the large blebs appear the diagnosis is evident. Vesicular and pustular *syphilitic* eruptions occasionally cause difficulty, but with a correct history few errors occur from this cause. In *molluscum contagiosum* the small tumors are not transparent and are filled with a soft granular substance easily squeezed from the tumor. There is not likely to be an associated fever, while in chickenpox with a large crop of vesicles slight fever is common. Acne very infrequently causes difficulty, but patches of *herpes* do so more commonly. With a magnifying glass the minute vesicles of herpes can be seen and the condition revealed.

The most important and difficult diagnosis is between a very mild form of smallpox and chickenpox. The differential points usually give a correct diagnosis, but there are cases in which at a given period and in the absence of a complete history a correct diagnosis is impossible. A short period of observation is required.

Prognosis.—In an uncomplicated case with a patient not exhausted by other diseases this is invariably good. If the patient is attacked by chickenpox during convalescence from some prolonged illness, such as scarlet fever, pneumonia, or diphtheria, and has a severe infection, death may result. In such cases there seems a distinct tendency for the varicellous lesions to become gangrenous. Erysipelas may appear during convalescence, due to infection of the lesions through scratching and has in several instances caused death. Nephritis during an attack is by no means uncommon, and the reviser has seen three instances of this complication in young children in the past three years.

Treatment.—The patient should be isolated or at least removed from the presence of susceptible persons until convalescence. There is a difference of opinion whether the remaining healthy children in a family should be deliberately exposed to infection when one child in the family is ill with the disease. Personally the reviser feels that with a child in good health it is quite as well to deliberately allow exposure early in life, as there is comparatively little danger if precautions are observed. If the disease is escaped in early life the patient is likely to contract it at a more awkward and inconvenient time; an attack in adult life is almost invariably more severe than in childhood. In those instances of weakly children or those suffering with or convalescing from prolonged illnesses it is dangerous to expose them to any infection even as mild as the usual case of chickenpox.

Rest in bed in a well-ventilated room with a low diet is the best rule to follow. Sometimes there are so few symptoms that it is difficult to keep children in bed. The finger nails should be cut short to prevent scratching, and at times the wearing of mittens is necessary. Local treatment to relieve the irritation and itching is the most necessary part of the treatment. Welch and Schamberg recommend the following lotion:

℞—Acidi carbolici	♏xxx to ʒj	2 to 4	0 cc.
Glycerini	ʒj	4	0 cc.
Spts. vini recti	ʒss	15	0 cc.
Aquæ	q. s. ad ʒvi	180	0 cc.

The addition of 10 grains of menthol or thymol sometimes increases the comfort of the patient.

When the vesicles become distended with cloudy material, particularly upon the face, it is well to evacuate the material and cleanse with a mild antiseptic lotion. The following ointment is useful in preventing secondary infection:

℞—Acidi carbolici	♏x	0	6 cc.
Hydrargyri. chlor. mit.	grs. xv	1	0 gm.
Pulv. amyli,			
Pulv. zinc. oxidi	āā ʒij	8	0 gm.
Petrolati	ʒss	16	0 gm.

CHAPTER XXV

SCARLET FEVER

By JOHN H. McCOLLOM, M.D.
AND
EDWIN H. PLACE, M.D.

Definition.—An acute febrile highly infectious disease characterized by an angina and a general punctate erythema. The types of the disease differ greatly in severity. The intensity of the eruption varies in a marked degree.

Occurrence.—In England and Germany the disease is always endemic and frequently epidemic. In the northern part of the United States scarlet fever is much more prevalent than in the southern portions. In the Northern States it has been noticed that about once in every five or six years there is quite a general epidemic of this disease which frequently assumes a malignant type. In the State of Massachusetts the death-rate of scarlet fever per 10,000 of the population from 1866 was as follows:

Years.	Deaths.	Death rate.
1866–1875	11,452	7.7
1876–1885	6,021	3.4
1886–1895	4,667	2.0
1896–1903	2,566	1.3

In Boston scarlet fever has always been prevalent, but in the past few years the ratio of mortality per 10,000 of the population has diminished very materially. Fig. 26 shows the ratio of mortality of scarlet fever per 10,000 of the population in Boston for sixty-five years, 1840 to 1904 inclusive. Previous to 1876 the average ratio of mortality was 11.22, while from 1877 to 1904 it was 2.61. Previous to 1877 there was a marked increase in the ratio about every five years, particularly noticeable from 1841 to 1857. From 1857 to 1876, although the average ratio was not so high, yet every two or three years there was a marked increase. From 1877 to 1895 the ratios were not particularly high, but the variation from a low rate to that of a comparatively high one was noticeable. Since 1895 the ratios were lower than in previous years, but there was still a certain amount of variation. For the years from 1902 to 1904 inclusive there was a diminution each year.

Etiology.—As scarlet fever is an infectious disease, the influence of climate on its prevalence cannot be very great, except indirectly. The habits of life in warm climates are so essentially different from those in temperate climes that scarlet fever is not so likely to gain a foothold in the former as in the latter. The aggregation of individuals is always an important factor and cities always suffer more than rural districts.

The tenement house increases the prevalence of the disease. In the United States, in cities where one family among the middle and lower classes occupies a small house, the disease is not nearly so common, as a rule, as in the cities where three or more families live in tenement houses. Where large numbers of children are brought into immediate contact, as in schools, scarlet fever is sure to prevail to a greater or less extent from the fact that there are always in any thickly settled community a certain number of individuals suffering from mild and unrecognized attacks. Fig. 27 shows the number of cases of scarlet fever in Boston by months, reported to the Board of Health for fifteen years, 1890 to 1904 inclusive, comprising 23,835 cases.

Fig. 26

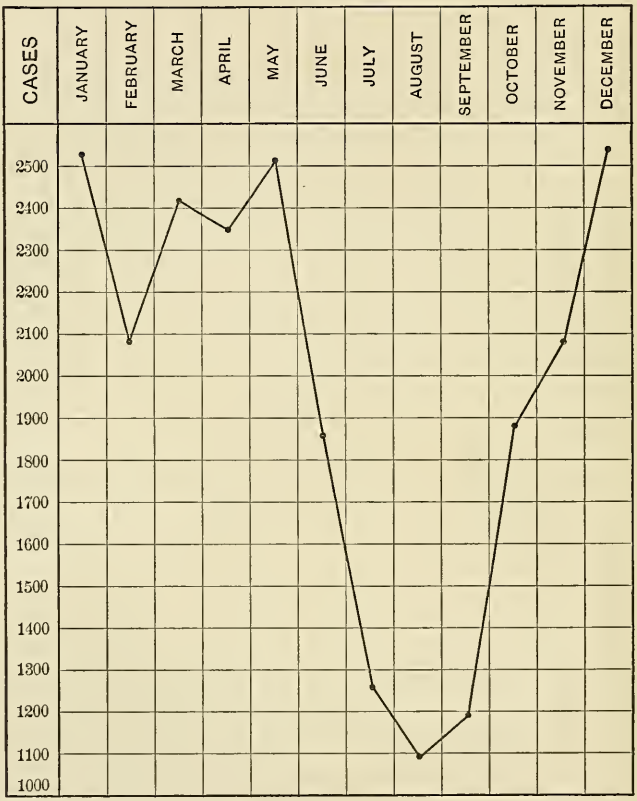
Ratio of mortality of scarlet fever per 10,000 of the population in Boston for sixty-five years, 1840 to 1904 inclusive.

During July and August, when the schools are not in session, the number of cases is very much less than during November, December, and January; the increase commences in September and there is a very marked increase from September to October, from October to November, from November to December; December and January are practically the same. There is a diminution from January to February, but no perceptible diminution in March, April, and May as compared with February. The number reported for the months of June in these fifteen years was 1863, while the number reported for the months of October for the corresponding years was 1883, practically the same, so that meteorological conditions can have no particular influence, except indirectly. The better that school-rooms and houses are ventilated, the less the possibility of infection. The majority of these cases of scarlet fever occurred in children of the school age. The importance of a medical inspection of schools, in order that children with mild attacks of the disease should be excluded, is evident.

Infectiousness.—While scarlet fever is extremely infectious, the degree of infectiousness is not so great as that of the other exanthemata. The

length of time of exposure necessary to contract the disease may be very short, as cases are on record, the accuracy of which cannot be doubted, in which the time of exposure could not have been more than one-half hour. Several have been observed by the writer in which the time of exposure varied from an hour to an hour and a half. In these instances, although the patients who contracted the disease were in the same room with cases of scarlet fever, they were not in immediate contact.

Fig. 27



Cases of scarlet fever in Boston, by months, reported to the Board of Health from 1890 to 1904.

The contact, as a rule, needs to be fairly intimate to allow infection of scarlet fever as contrasted with measles or whooping cough. There are many apparent instances of infection persisting on infected articles for months or years, but these must be discounted because of the difficulty of excluding other manner of infection. The virus is resistant outside the body, but until animal inoculation is available its viability must remain uncertain.

The *specific cause* has so far been undiscovered. There are three chief theories regarding the etiology: (1) streptococcus; (2) protozoön; (3) filterable or ultramicroscopic virus.

1. *Streptococcus.*—The work of Baginsky, D'Espine, Moser, Meyer, Schleissner and others has supported the streptococcus as the cause, while that of Heubner, Marmorek, Jochmann, Slawyk, Pearce, Weaver, and Hektoen is against this. That the streptococcus is practically always associated with scarlet fever both in the throat and in the septic complications is generally accepted. Page found streptococci in the throats of 23 of 24 patients. Weaver (1903) found the streptococcus practically always present in the throats of scarlet fever patients, especially early in the disease, and found that they resisted drying longer than other associated bacteria. He did not find any difference in these streptococci from those of other infections. Schleissner (1909) found streptococcus in all throats in the early stage and in the blood in a large proportion of the cases. In practically all the local and general septic complications streptococci are found, as in the joints, bursæ, abcesses, sinuses, etc., and usually in pure culture. Recently in 60 cases of scarlet fever at the Boston City Hospital, examined by Floyd, the blood taken during life or immediately postmortem showed streptococci in 12 or 20 per cent. These could not be differentiated from other streptococci centring culturally about the group of pyogenes, although two resembled the *Streptococcus salivarius*. The opsonic index (Tunnecliff) for streptococci in scarlet fever has been found to follow the clinical course, being low in the acute stage and with complications and rising with convalescence, and this is specific for the streptococcus. This does not demonstrate an etiological relationship more than a secondary invasion.

Much work has been done on complement fixation and agglutinins, and while the results vary, the evidence fails to support the belief that the streptococcus in scarlet fever is essentially different from that of other infectious processes. The reputed specific benefit from antistreptococcus serum in the cure of scarlet fever has no particular bearing on etiology, as it is generally acknowledged that the streptococcus plays an important part in the complications and mortality.

The only evidence bearing especially on the etiological role of the streptococcus is the results obtained by streptococcus immunization against scarlet fever by Gabritschewsky and his pupils, chiefly, in Russia. This is not conclusive because of the great variation in the incidence and severity of scarlet fever and the influence of other measures.

It is well known clinically that certain septic conditions, as puerperal sepsis, due to streptococci, present rashes, and are followed by complications simulating scarlet fever, sometimes indistinguishable, and that these conditions do not spread scarlet fever. Gabritschewsky also noted in some of the immunized cases, rashes, fever, sore throat, strawberry tongue, and even complications as hematuria, which could not be differentiated from those of mild scarlet fever, although there was no evidence of contagion. The facts that streptococci play an equally important part in smallpox, etc., and that streptococcic diseases, as erysipelas, do not give a lasting immunity; that no clear differentiation by agglutinins, complement fixation, or special cultural studies, as hemolysis and sugar-splitting, has been demonstrated, make the etiological relation of the streptococcus very doubtful. Further knowledge of the biology

of the streptococcus group is needed to be certain that one species is not the cause, but at present it cannot be so held.

2. *Protozoön.*—The finding of protozoön-like bodies in the skin and mucous membranes by Mallory, Duval, Siegal, Prowazek, Gamoleia and Schick, and Rach have drawn attention to this possibility. Field has found similar bodies in other conditions, and there is not sufficient evidence to prove at all conclusive.

3. *Filterable Virus.*—Bernhardt[1] claimed to have transmitted the infection to the lower monkeys by filtrates free from recognizable bacteria. Cantecuzene also found that on repeated transmissions through lymph nodes, he secured nodes, emulsions of which produced scarlet fever, although free from streptococci. This seems to agree with the known facts of scarlet fever and the diseases produced by filterable viruses, as measles, foot and mouth disease, etc. As in hog cholera, the association of the hog cholera bacillus with a filterable virus and the relation of the bacillus to the lesions is similar to what may occur in scarlet fever.

The possibility of a symbiosis, a necessary association of two factors in the cause cannot be excluded but still is highly theoretical. There is a question as to how many of the symptoms of scarlet fever, as the throat, rash, etc., are due to streptococci instead of the scarlet fever virus *per se.* There can be no question that much of the throat involvement, especially in the severer cases, is due to the streptococcus. Rashes occur in certain cases of sepsis which are indistinguishable from those of true scarlet fever.

It seems probable that scarlet fever poison causes inflammation of the throat just as measles causes a more diffuse involvement of mucous membranes and that this makes a favorable condition for secondary infection. It also seems probable that the scarlet fever virus has a special action on the skin and kidneys and possibly on the endocardium and pericardium.

Scarlet Fever in Animals.—There is no evidence of natural scarlet fever in any of the domestic animals. Lower monkeys have apparently been infected, but negative results have been obtained by many observers, and it seems probable that the lower animals are practically immune. The clearest case of animal scarlatina was that obtained by Landsteiner, Levaditi and Prazek (1911) by inoculation of chimpanzees with blood and mucus from the throat and lymph nodes. One ape had sore throat, strawberry tongue, rash, and desquamation.

Susceptibility.—Age.—The incidence of hospital cases according to age is shown by the accompaning table:

Under 1 year	42	9 to 10 years	250
1 to 2 years	182	10 to 11 years	202
2 to 3 years	381	11 to 12 years	143
3 to 4 years	569	12 to 13 years	120
4 to 5 years	551	13 to 14 years	81
5 to 6 years	557	14 to 15 years	48
6 to 7 years	522	15 to 18 years	125
7 to 8 years	424	18 to 23 years	245
8 to 9 years	323	Over 24	235
		Total	5000

[1] *Deutsch. med. Wochschr.*, March 17 and April 27, 1911, xxxvii, No. 17.

Under one year the disease is not infrequent. The youngest case we have seen was that of a baby admitted to the scarlet fever ward with the mother who had scarlet fever on the second day of the puerperium. This infant was not nursed except for a few days and developed inflamed throat, brilliant rash, high fever with lysis followed by otitis media on the tenth day after admission and at two weeks of age. Kerley noted four cases of nursing babies who failed to contract scarlet fever, although twenty-two older children and one of the mothers under the same conditions did. There is a relatively low incidence after eight years and after fifteen years much lower. There is unquestionably a less susceptibility to scarlet fever than to measles, but it is not improbable that this may be due partly to differences in the ease of transmission of the two viruses, instead of purely specific immunity.

Thorough intimate exposure often produces a much higher incidence than usually occurs. Kerley noted that twenty-two of twenty-six children continuously exposed developed the disease, the four escaping being nursing infants. We have known eight of ten children to contract the disease from a patient with dischage from the nose and ears after a prolonged intimate exposure.

Adults are less frequently attacked, and this seems to be due to actual immunity. The incidence of scarlet fever among 625 nurses in our wards in the past ten years has been only 2 per cent. as contrasted with 30 per cent. for diphtheria. Of the medical students who attend clinics in the hospital only about 20 per cent. have a history of scarlet fever (about 90 per cent. give a history of measles) and only three have contracted the disease in the past eight years, one during an extensive epidemic in the city.

In milk-borne epidemics there is usually noted an unusually large percentage of adult cases, which suggests that part of the low incidence in adults is due to lack of exposure in ordinary life.

Manner of Spread.—Scientific proof of this and the points of ingress and egress of the virus is still lacking, owing to the difficulty in infecting animals. Clinical studies have shown that the disease is spread through the secretions of the nose and throat both during the early stage and late into convalescence. It is also spread through discharges, at least in some cases, from the ear and other lesions of the cutaneous or mucous membrane surface.

The disease is infectious from the first lesion of the mucous membrane until the membranes are completely healed, sometimes many weeks (twenty), into convalescence. Children, as a rule, who develop the disease in hospital wards and are isolated at once rarely transmit the disease to others. When missed cases are admitted and come into intimate contact with other children for some time other cases are frequent. If the missed patient is too ill to be up or to play with other children, often the disease is not transmitted. In one case a child with an abscess of the neck remained in the children's surgical ward for a week without other cases developing, although the nurse who did the dressings came down with the disease. This patient was desquamating and his brother was admitted to the contagious hospital shortly after. He had been taken

ill with characteristic symptoms one week before the abscess required surgical treatment.

There is no evidence that the desquamating skin contains the contagium itself, although no proof can be brought to bear as to its utter innocuousness. The common belief in its contagiousness apparently was due to the frequency of desquamation, and the mistaken idea that the period of contagion corresponded with the period of desquamation. The spread of the disease does not follow the lines suggesting exfoliating epidermis. There is almost certain evidence that scarlet fever does not spread through the air but requires some direct contact with the contagion carrier or with some object with which he has been in intimate contact. There is no development of the disease around foci, as contagious hospitals. Patients who remain free from direct or indirect contact with the disease apparently escape when the air circulation is free.

Missed cases and "carriers," those who have recovered but still harbor the contagion, especially in the nose, are important factors in the spread. It is not known whether those who have not had the disease may harbor the contagion as in diphtheria, but the evidence is against this.

Milk has been an important factor in some epidemics, especially in England. Greater Boston suffered severely in 1907 with 717 cases and in 1910 with 842 cases. The milk-epidemics are characterized by a rather large percentage of adults, a very sudden rise in the incidence, and often with an increase in the severity.

Pathology.[1]—The gross pathological lesions are slight. The diffuse exanthem of the skin and the rash often present in the mucous membrane covering the tonsils, palate, and cheeks usually do not show after death. A false membrane on the tonsils may occasionally be seen. Desquamation is often evident if death occurs in the later stages. The only constant gross change found postmortem is a hyperplasia of the lymphoid tissue in every part of the body. On the other hand important lesions may occur in certain organs as sequelæ or complications.

The lesions of the skin are interesting histologically. The bloodvessels of the corium show marked dilatation, more especially near the epidermis and in the papillæ. The superficial lymphatics and lymph spaces likewise show dilatation in the same situation, that is, just beneath the epidermis and in the papillæ. The exudative phenomena which take place in the skin vary with the intensity of the disease. They may be slight or very prominent. In a well-marked case the leukocytes are abundant in the dilated bloodvessels of the corium, and many have emigrated from the bloodvessels and can be found in the corium and invading the epidermis. They consist chiefly of polymorphonuclear and endothelial leukocytes, but lymphoid cells and rare eosinophiles are found among them. The

[1] The section on Pathology was written by F. B. Mallory, M.D. This account of the pathology of scarlet fever is based in part on the paper by Dr. R. M. Pearce (Scarlet Fever, its Bacteriology, and Gross and Minute Anatomy, *Medical and Surgical Reports of the Boston City Hospital*, 1899, x, 39 to 82) and in part on the study of the same cases which he used and of other cases which have come to autopsy at the Boston City Hospital since his paper was published.

EXPLANATION OF FIGURES IN PLATE XXXI

The drawings were made with the Abbe camera lucida; projection on to table. Zeiss apochromatic homogeneous immersion 2.0 mm., apert. 130, compensation ocular 6.

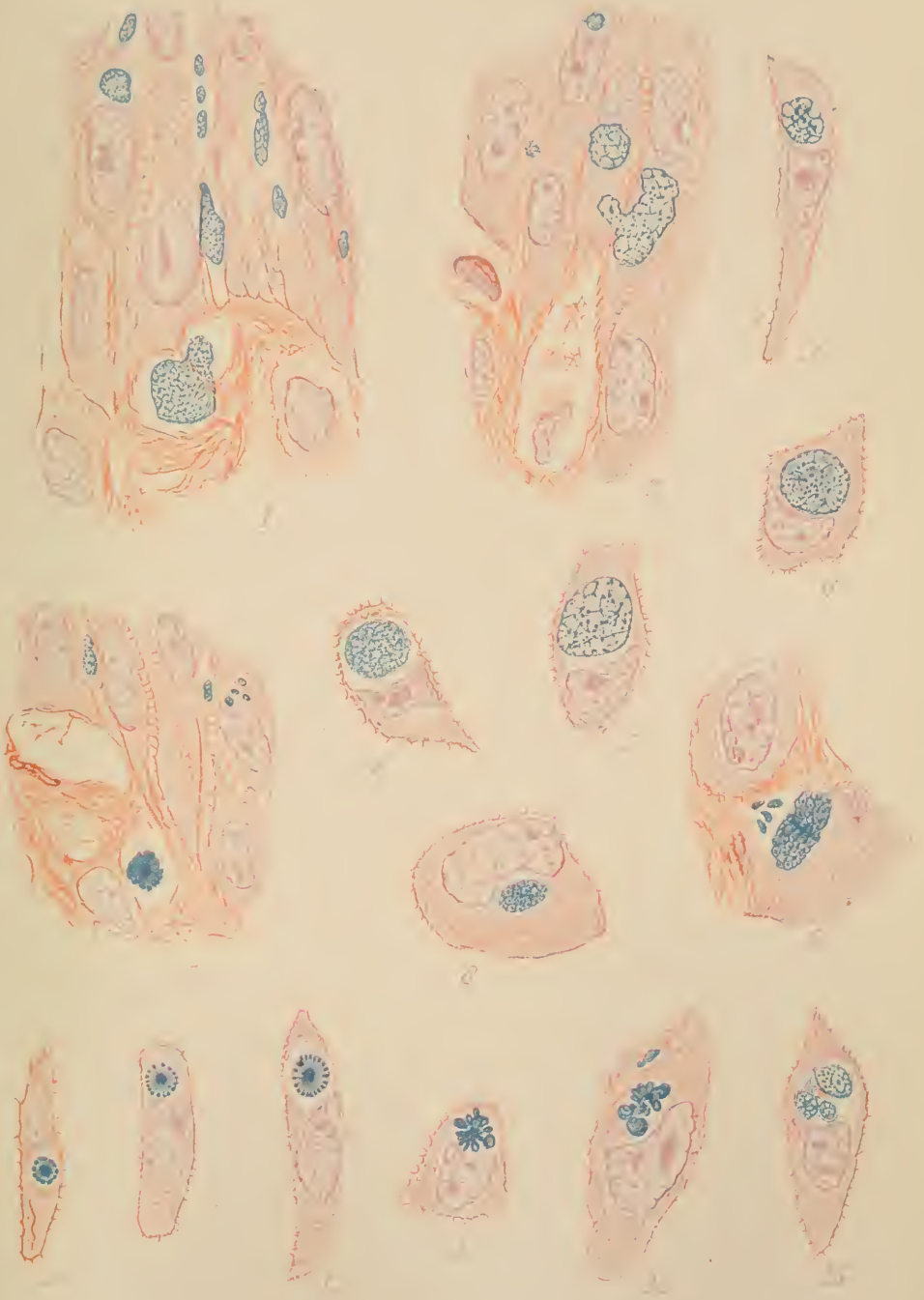
Figs. 1 and 2 show numerous large and small scarlet fever bodies (stained light blue) in and between the epithelial cells of the rete mucosum. In Fig. 1 is a large body in a lymph space of the corium just underneath the epidermis. Several of the bodies suggest fixation while in amœboid motion.

Figs. 3, 5, and 6 are coarsely reticulated forms which may be degenerated forms of the scarlet fever bodies, or stages in sporogony.

Figs. 4, 8, and 9 probably represent stages preceding the radiate bodies. In Fig. 9 the bodies lie in a lymph space. It shows also four small forms which have just got free from a rosette.

Figs. 7, 10, 11, 12, 13, 14, and 15 show different stages in the development of the radiate bodies.

Fig. 10 is the earliest stage: there is a distinct central body and a definite, regular arrangement of granules at the periphery. Figs. 7, 11, and 12 show a little later stage of development; 11 and 12 are optical sections, while 7 is a surface view. Moreover, in Fig. 7 the body lies free in a lymph space in the corium. The segments begin to show a certain amount of lateral separation from each other. Fig. 13 is a still later stage: the segments are increasing in size and are more or less free from each other, although most of them are still attached to the central body. In Fig. 14 the segments are all free and enlarging, although still grouped around the central body. In Fig. 15 the bodies are still grouped around the central body, which is free and stains deeply with eosin. (Mallory.)



leukocytes are collected around the blood- and lymph vessels and also in the tips of the papillæ. The lymphatics contain serum and an occasional leukocyte. In the epidermis the leukocytes are usually elongated and distorted, owing to fixation while in amœboid motion between the epithelial cells, but some show a greater or less degree of necrosis.

The epidermis shows but slight changes beyond swelling of the cells in the stratum lucidum in consequence of œdema: the limits of the cells are well defined, but the cytoplasm is reticulated and the nucleus often lies in a vacuole. Occasionally elsewhere in the epidermis a necrotic epithelial cell is found. In contrast to these degenerative changes many mitotic figures are present in the rete Malpighii. The inflammatory exudation continues for several days, and is, perhaps, most abundant in those cases which die on the fifth to the tenth day from the onset of the eruption. By the twelfth to the sixteenth day the leukocytic infiltration has nearly disappeared.

In the *tongue* the pathological changes are similar to those in the skin, but they begin earlier and are more marked. There is the same dilatation of the bloodvessels and lymphatics in the corium and an abundant infiltration both of the corium and of the epithelium with polymorphonuclear leukocytes. The infiltration is always greatest in and over the papillæ, and affects the papillæ more at the tip than at the base of the tongue. The mucous membrane of the *pharynx, soft palate,* and *tonsils* shows changes similar to those in the tongue.

These degenerative and exudative phenomena in the skin and mucous membranes probably represent the primary essential lesion of scarlet fever. The discovery[1] in the skin of scarlet fever cases of bodies which resemble protozoa is interesting and possibly of much etiological significance. The bodies usually vary from 2 to 7μ in diameter, but occasionally measure 10 to 12μ. They may be divided into two sorts, the granular and the radiate. The granular bodies are usually finely but occasionally coarsely meshed and show all variations in size between the limits given. They often contain one or more small but distinct vacuoles. They vary in shape from round to elongated and lobulated forms suggesting amœboid motion. The radiate bodies vary in diameter from 4 to 6μ and are almost invariably spherical in shape. They contain a central round body, around which are grouped on optical section 10 to 18 narrow segments which in some cases are united, but in others are sharply separated laterally from each other. Occasionally some of the segments are larger than the others, and in their staining reaction and form closely resemble the smallest granular bodies. Sometimes all the segments are seen as small free bodies which still surround the central body, or seem as if they had been fixed while moving away from it between the cells. (Plate XXXI.)

These two kinds of bodies are found in three situations: lying in vacuoles in the epithelial cells of the epidermis, to a less extent between these cells, and free in the lymph vessels and spaces of the corium just beneath the epidermis. When within epithelial cells they usually cause

[1] Mallory, F. B., Scarlet Fever; Protozoön-like Bodies Found in Four Cases, *Journal of Medical Research*, 1904, v, 483 to 492.

indentation of the nucleus. The bodies are not distributed evenly, but usually occur in small clumps. Moreover, the skin from one location may show them chiefly in the lymph spaces of the corium, especially in the papillæ, while in that from another situation they may be almost entirely between or in epithelial cells. They are always least numerous where leukocytes are most abundant.

At the time of the first description of these bodies they had been found in skin taken probably from over the chest or abdomen. Since then Duval has found them in more recent cases which have come to autopsy. The bodies were present in skin from the chest, abdomen, groin, and inner aspect of the arm. Led by their presence in the lymph vessels and between the epithelial cells of the epidermis to the belief that the bodies might be drawn out with the serum, he devised a simple method[1] of producing rapid vesication and was able to obtain the bodies often in large numbers from vesicles produced in the groin in five out of eighteen cases. The serum was practically free from cells and the bodies could be stained in cover-slip preparations.

It is doubtful if these bodies are degenerations, because they occur not only within cells but free between them and within lymph spaces of the corium. It seems much more probable that they are protozoa and have an etiological relation to scarlet fever.

Lesions due to secondary infections with the *Streptococcus pyogenes*, less often with staphylococci or pneumococci, are relatively common and complicate the changes due to the causal agent of scarlet fever. These secondary processes are, in the order of their frequency: acute bronchopneumonia, acute inflammation of the middle ear with or without extension to the mastoid cells, suppuration of cervical lymph nodes, acute pleuritis, and inflammation of the antrum of Highmore. The less frequent complications are abscess of the lung, ulceration and abscess formation in the upper respiratory tract, acute endocarditis, inflammation of the sphenoidal sinus, and metastatic abscesses of the kidney.

The bronchopneumonia may occur as small discrete or as large confluent nodules. Areas of atelectasis are often associated. Microscopically the exudation does not differ from that in bronchopneumonia in other infectious diseases, except, perhaps, in the number of plasma cells present. They usually occur in small numbers among the other elements of the exudation, but are found in greater abundance in the walls of the alveoli. They are also often present in the bloodvessels. In all these situations their nuclei often show mitosis.

Acute inflammation of the *middle ear* occurs in many cases and is usually bilateral. Rarely the process extends to the mastoid cells. In the majority the exudation is purulent, but in others it is mucoid with an abundant mixture of pus cells. As a rule the infection is due to streptococci and may occur as early as the third day. Less often a similar infection of the *antrum of Highmore* and still more rarely of the *sphenoidal sinus* may take place, with a purulent or mucoid exudation.

A general infection or *septicemia*, usually streptococcic, is of common

[1] Duval, C. W., Die Protozoen des Scharlachfiebers, *Virchow's Archiv*, 1905, clxxix, 485 to 498.

occurrence. As a result it is difficult to determine in all cases just what part of the systemic lesions present in the different internal organs is due to toxic substances derived from the infectious agent of scarlet fever and what part to the toxic substances derived from the bacteria present as secondary invaders. Still a certain number die from uncomplicated scarlet fever, and from these a true picture of the systemic lesions caused by the scarlet fever organism can be obtained. Like the general systemic lesions in diphtheria they are characteristic but not specific.

The muscle fibers of the *heart* in a certain proportion of cases show degenerative changes, of which the most important is that associated with the deposit of fat in fine droplets in the fibers.

Ordinarily the *spleen* is not enlarged. It is firm, and the capsule is smooth but not tense. There is no increase of pulp, but the Malpighian bodies usually are decidedly enlarged and stand out prominently as gray to white areas on a dark reddish background. In some cases, however, the spleen is enlarged and soft, the pulp greatly increased, and the Malpighian bodies indistinct. The cause of these differences is not apparent. *Microscopically*, in stained preparations the centres of the enlarged Malpighian bodies appear pale, while the periphery is stained deeply. The pale centres are composed chiefly of large phagocytic cells derived by proliferation from the endothelial cells lining the reticulum of the lymph nodules. The lymphoid cells in the centres of the nodules have for the most part been incorporated and digested by the phagocytic cells in whose cytoplasm only fragments of them can be found. The phagocytic cells are usually more or less fused together so that their outlines are made out with difficulty. In some cases they undergo necrosis and are transformed into a hyaline material which stains deeply with eosin. The deep staining of the periphery of the Malpighian bodies and, aside from the phagocytic cells, the chief cause of their enlargement are due to the presence of great numbers of plasma cells, many of which show mitosis. The infiltration with plasma cells likewise occurs abundantly everywhere in the pulp.

The veins of the spleen often present a curious condition. Collections of cells take place beneath the lining endothelium and in some cases cause irregular projections into the lumina so as almost to occlude them. The cells which collect in this manner are principally lymphoid and plasma cells.

The changes in the *gastro-intestinal tract* are slight and mostly due to secondary infections. Ulceration of the œsophagus and small abscesses in the mucous membrane have been noted. Hemorrhage may occasionally be found beneath the mucous membrane of the stomach and intestine. The one constant lesion is a more or less well-marked hyperplasia of the lymph nodules of the intestine. In severe attacks with death early in the disease, the Peyer's patches are exceedingly prominent, and the swelling may be almost as marked as in typhoid fever. The solitary lymph nodules of the large intestine may be equally prominent.

In the lymph nodules of the *intestine* there is a marked proliferation of endothelial cells in the centres and a corresponding disappearance

of the lymphoid elements which have been incorporated and digested. In the *appendix* the lymph nodules show a marked degree of the same process.

The changes in the *liver* are usually slight and chiefly of a degenerative character—fatty degeneration being the most important. Necroses occur rarely; two types have been observed, the central and the focal.

In the *kidneys* acute degenerative changes are common, especially cloudy swelling and fatty degenerations. The most interesting and important lesion is acute interstitial non-suppurative nephritis, which is fairly common. The process varies from slight to very extensive changes. In marked cases the kidneys are enlarged and the capsule peels readily, leaving a smooth, pale, watery surface. On section the cortex is swollen and the cut surface is mottled with small grayish, translucent areas, most numerous in the intermediate zone and in the adjoining cortex. These areas are irregular, round, or linear in shape. They are present in a less degree in the cortex immediately beneath the capsule. Small hemorrhages may occur here and there.

Histologically the process consists of a cellular infiltration, most marked in the cortex just beneath the capsule, around the glomeruli, and around the bloodvessels in the intermediate zone. The cellular areas are composed chiefly of plasma cells, but a certain number of lymphoid cells and polynuclear leukocytes are usually associated with them. Many plasma cells are also found in the straight vessels of the pyramids. It is evident that they migrate from these vessels into the adjoining tissue. The degenerative changes in the renal epithelium are no more marked in these cases of acute interstitial nephritis than in those in which no interstitial changes are present. Although acute capsular glomerulonephritis is generally believed to occur not infrequently after scarlet fever, no case of it has yet been observed in the rather large series of autopsies at the Boston City Hospital.

The *lymph nodes* in all situations are enlarged, firm, and on section pale and watery. They are never soft and pulpy unless secondarily infected. The cervical lymph nodes show the greatest enlargement, the axillary and inguinal the least. The changes in them are not constant in all cases, but in general they are similar to those in the lymph nodules of the spleen. The bloodvessels are congested. The lymph sinuses are dilated and contain many large endothelial cells which are frequently phagocytic. The inclusions are generally lymphoid cells and red blood corpuscles, and may be very numerous, ten to twenty in a cell. The sinuses also contain numerous plasma cells. The lymph nodules are much enlarged and contain in their centres numerous large, lightly staining, endothelial cells, which are so closely packed together that their outlines are usually made out with difficulty.

The chief change in the *bone-marrow*, aside from numerous eosinophiles, is the presence of great numbers of cells which cannot be distinguished from plasma cells. They frequently show mitotic figures and correspond in every way with the cells found in the bloodvessels everywhere and in the interstitial tissues of the kidneys.

The other organs of the body are negative, except that the *thymus*

gland in some cases contains many phagocytic cells in which are incorporated lymphoid cells and red blood corpuscles.

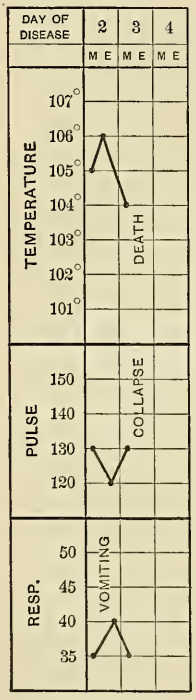
Incubation.—There is a marked difference in opinion regarding the incubation stage, some giving as short as twenty-four hours, others as long as twenty-one days. Much of this discrepancy is due to faulty observation, and also to the fact that, although there may be a certain definite known exposure to the disease, there is also just as likely to be an unknown exposure to a mild and unrecognized attack of scarlet fever. The question arises as to why scarlet fever should have a much shorter period of incubation than other infections. In a few instances where individuals have been inoculated with the blood of scarlet fever patients, it has been found that three or four days elapsed before the onset of symptoms. This would seem to be a sufficient answer to the statement that the period of incubation of scarlet fever may be twenty-four to forty-eight hours. When a patient in a hospital has an attack of scarlet fever and is removed as soon as the diagnosis is made, other patients in the same ward, if susceptible, do not show any symptoms for at least a week or ten days, and, in some instances, twenty days. At the South Department, of the seventy-four nurses who contracted scarlet fever when on duty, in only one instance was the period of incubation as short as six days. It may be said that a person exposed to scarlet fever does not always contract the disease at once, but if the period of incubation is so short as twenty-four or forty-eight hours, certainly some of these individuals would have contracted the disease in that time. Quite a number of instances have come to the knowledge of the writers where it was definitely known that there was only one exposure to scarlet fever and where the disease became manifest twenty days after this. It is a very frequent occurrence for a child of the school age to be admitted to the South Department ill with scarlet fever and the other children in the same family too young to attend school do not show any symptoms of the disease for a week or ten days. This has been of such frequent occurrence that it suggests that the period of incubation cannot be as short as twenty-four hours.

Hagenbach-Burkhardt reports 57 cases in which he gives the incubation period of 35 cases as over seven days, under eight days 4 cases, nine days 2 cases, ten days 1 case, eleven days 5 cases, twelve days 1 case, thirteen days 4 cases, fourteen days 2 cases, fifteen days 5 cases, seventeen days 2 cases, eighteen days 1 case, nineteen days 2 cases, and over twenty days 6 cases. Veit says that the period of incubation may be twelve to fourteen days. Paasch reports a case in which it was twelve days. Gerhardt and Reinhold give eleven to thirteen days. Bawy reports a case in which the period of incubation was twenty-one days; Trojanowsky one in which it was twenty-eight days. Where there is a difference of opinion regarding the period of incubation it is evident that these different observers cannot be all correct or all incorrect. The most logical conclusion is that the mean time of these different observers, twelve to fourteen days approximately, is probably the true period of the incubation. From the study of over 5000 cases of scarlet fever, in many of which the time of exposure was definitely known, the writers are

thoroughly convinced that the period of incubation is variable; that the limits are practically from four to twenty days, with an average of ten to fourteen days.

Symptoms.—Five distinct varieties of the disease are recognized. *First,* the fulminating, in which the patient succumbs in from twenty-four to forty-eight hours. This is frequently mistaken for hemorrhagic smallpox and, on the other hand, hemorrhagic smallpox is mistaken for it. Persistent vomiting is a prominent symptom; diarrhœa frequently occurs. The angina is not particularly marked. If the patient dies within twenty-four hours the characteristic eruption does not appear, and the diagnosis must be based on the constitutional symptoms. If the patient lives forty-eight hours there is a very general erythematous blush, but the eruption does not assume the characteristic appearance because the patient does not live long enough. The erythema is an extremely brilliant red, and in some instances the skin is almost a mahogany color. Delirium of a violent type is a prominent symptom. The temperature is extremely high, from 105° to 106° F. (Fig. 28). *Second,* a malignant form, in which the temperature is extremely high from the outset, frequently reaching 105° F. (Fig. 29). The eruption is extremely brilliant, and it is impossible to make out the punctate appearance except in small areas scattered here and there. Delirium of an active type, and in some instances of the low muttering variety, is usually present. There is marked dysphagia and sometimes so much swelling of the fauces as to interfere with respiration. The tongue is heavily coated. *Third,* a moderately severe variety, in which the temperature reaches 104° (Fig. 30). There is a profuse nasal discharge and marked anginose symptoms. *Streptococcemia* is always present in this form. The patient, as a rule, is not actively delirious but in a state of semistupor. The eruption is not extremely brilliant, but has the characteristic punctate appearance. *Fourth,* a form characterized by a certain amount of angina, a not particularly high temperature (Fig. 31), a somewhat faint but characteristic punctate eruption on the body and in the roof of the mouth. The eruption is accentuated in the axillæ and in the groins. *Fifth,* a variety in which the anginose symptoms are particularly marked, and the cutaneous manifestations in abeyance. This variety has been termed *scarlatina sine eruptione* (Fig. 32). There is no sharp and dividing line between these different varieties, but to understand the disease it is necessary to make this arbitrary division. Scarlet fever varies more in intensity than any of the other exanthemata, and this is the reason why the disease is so prevalent, as many cases are not recognized and therefore not isolated.

Fig. 28



The *onset,* as a rule (to which there are many exceptions), is abrupt.

The attack may commence with a slight headache, a feeling of chilliness not amounting to a rigor, a slight sore throat, nausea, and vomiting. In children the attack frequently begins with a convulsion. In some instances there may be a feeling of malaise for three or four days before

FIG. 29

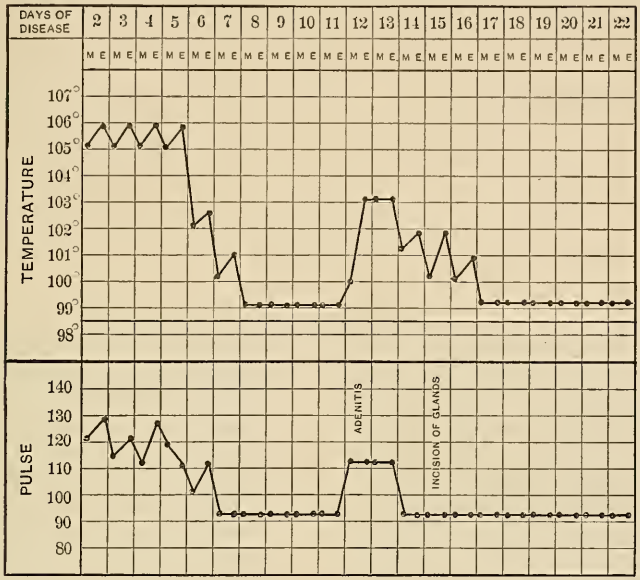
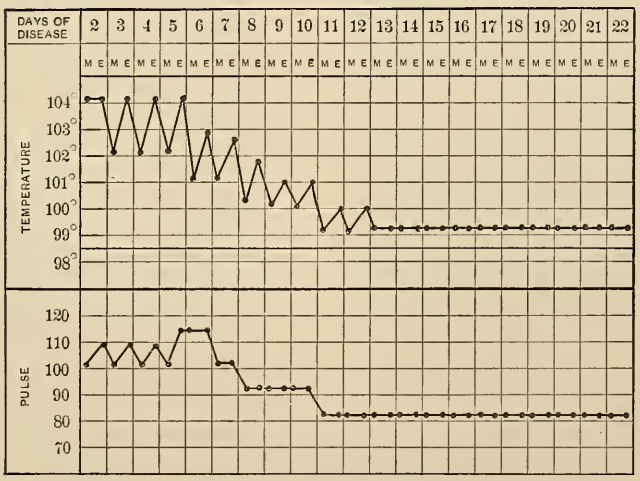

DAYS OF DISEASE
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E
TEMPERATURE
107° 106° 105° 104° 103° 102° 101° 100° 99° 98°
PULSE
140 130 120 110 100 90 80
ADENITIS
INCISION OF GLANDS

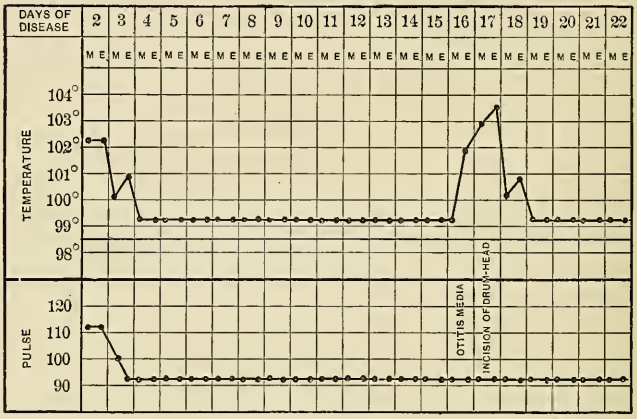
FIG. 30


DAYS OF DISEASE
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E
TEMPERATURE
104° 103° 102° 101° 100° 99° 98°
PULSE
120 110 100 90 80 70

the onset of the characteristic symptoms. Of 5000 cases observed at the South Department of the Boston City Hospital, nausea and vomiting as an initial symptom occurred in about 80 per cent. In 10 per cent of the remaining cases the patients were too ill to give any history.

Some observers have given the percentage of initial vomiting a little lower. It is reasonable to conclude that in about three-fourths nausea and vomiting are the initial symptoms. The characteristic eruption which commences, as a rule, on the chest may appear two or three hours after the vomiting or may be deferred for twelve to forty-eight hours. *Angina* of greater or less severity is present, as a rule, in every attack. It may be so slight as to escape detection or so severe as to be mistaken

FIG. 31


DAYS OF DISEASE
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
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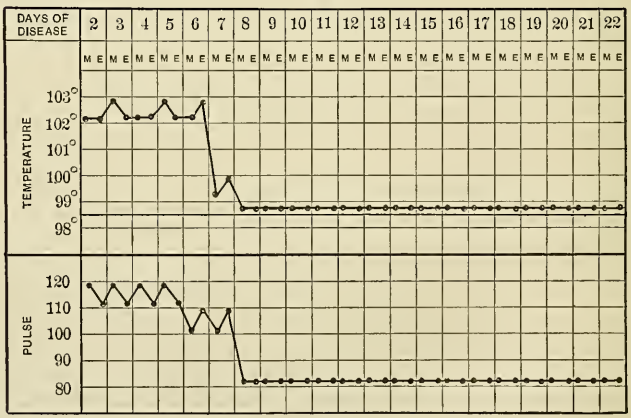
TEMPERATURE
104°
103°
102°
101°
100°
99°
98°
PULSE
120
110
100
90
OTITIS MEDIA
INCISION OF DRUM-HEAD

FIG. 32


DAYS OF DISEASE
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E
TEMPERATURE
103°
102°
101°
100°
99°
98°
PULSE
120
110
100
90
80

for diphtheria; an exudate which has a certain similarity to that of diphtheria frequently appears on the tonsils. The uvula is intensely congested and frequently œdematous. A punctate eruption is frequently observed in the roof of the mouth. The tongue is frequently coated with a creamy white fur through which the papillæ can be seen, giving the appearance known as the strawberry tongue. The *enlargement* of the papillæ of the tongue at the tip and edges is a constant symptom, and if a careful examination is made will be found in every case, although

in some instances it is so slight that it escapes detection. After the tongue is clean the papillæ become more prominent and look like minute buttons studding the surface. In the interspaces the mucous membrane is reddened and has a peculiar glazed, wrinkled appearance. In some instances the tongue looks as if it had been varnished, it is so smooth and dry. The papillæ sometimes have an appearance very much as if small grains of cayenne pepper had been sprinkled on the surface of the tongue. The circumvallate papillæ, always more or less prominent, do not seem to be especially increased in size, but it is the papillæ at the tip and edges of the tongue that present the appearance just described. The importance of the appearance of the tongue in diagnosis is very great, and frequently after the disappearance of the eruption and before desquamation takes place is the only symptom on which reliance can be placed. The figures (Figs. 33 and 34) are diagrammatic, and therefore the enlargement of the papillæ is exaggerated.

Fig. 33

Papillæ of the tongue about the third day.

Fig. 34

Papillæ of the tongue on the ninth day.

The history of a typical attack of scarlet fever of an extremely mild form is as follows: The child has a sudden attack of vomiting, complains of slight headache, but after vomiting seems to feel better. Five or six hours later the body is covered with a slight erythematous blush, with a faint punctate appearance. This fades in twelve hours, sometimes in six, and the child is apparently well. There is no isolation, and five or six days later other members of the family have attacks of scarlet fever of more or less severity. If the child goes to school he infects some of

his schoolmates. Some few years ago a child in an institution where there were 150 children had an attack of scarlet fever similar to the one just described, and infected 25 of the inmates. No physician was called, as the child apparently was not ill; the rash was so evanescent that it escaped the observation of the matron. The writer has seen some eight instances of outbreaks traced to similar mild attacks.

As scarlet fever varies in intensity, so does the temperature. As a rule, the more brilliant the eruption the higher the temperature. In a study of 3000 cases it was found that 102 had a temperature of 99° F., 411 has a temperature of 100°, 470 a temperature of 101°. In 589 the temperature reached 102°; it was 103° in 575 cases; it was 104° in 484 cases; in 330 cases it was 105°; and in 39 instances it was 106°. In 2487 cases the temperature remained above 100° one day in 414, two days in 558, three days in 498, four days in 315, five days in 204, six days in 153, seven days in 102, eight days in 114, nine days in 45, and ten days in 84 cases. The temperature in some cases falls by crisis and in others by lysis.

Eruption.—This is a punctate erythema and varies in a marked degree according to the type of the disease; sometimes the entire surface of the body is of a brilliant scarlet hue and it is impossible to make out the individual puncta. In other cases in certain portions of the body there will be simply a blush, and in other portions distinct puncta can be distinguished. In moderately severe attacks there is a marked redness of the palms and soles which have a hard and dry feeling. Numbness of the hands is not infrequent. As a rule, the eruption is accentuated on the axillæ, groins, popliteal spaces, and inner sides of the arms and thighs. The papillæ of the skin are enlarged in moderately severe attacks. Miliary vesicles frequently appear, although this is not a part of the disease but due to the high temperature. The small milky vesicles are most frequently on the neck, axillæ, or groins, but may be general, producing a very peculiar appearance. This miliary scarlet fever always has marked symptoms, but has a good prognosis. The skin has a peculiar harsh and dry feel, which is particularly marked after the fading of the eruption, or, in other words, the skin of the patient, if a child, resembles that of an old person. It has a papery feel, and wrinkles when the hand is passed across the abdomen. In the colored race there is a peculiar appearance of the skin which it is impossible to describe, the hue being of a more intense black and without the luster seen in health. The rash is sometimes markedly limited to the axillæ, groins, and sides of the chest or the inner sides of the arms and legs, but it is practically always symmetrical. In some cases it is very intense in these areas and only slight on other parts of the skin. It is not unusual to find a coarse blotchy rash on the forearms and legs, especially the extensor surfaces, but on the body such blotchy rashes do not occur.

The eruption generally commences on the trunk and extends upward to the neck and downward to the extremities. As a rule, there is no eruption on the face. The cheeks may be extremely red, but the upper and lower lips are pale, giving the appearance known as mouth pallor, which is a very constant symptom in moderately severe attacks.

PLATE XXXII

Scarlet Fever. Stage of Eruption.

Frequently there is an intense burning heat of the skin, sensible to the touch, although the temperature may not be particularly high. As the character of the disease varies greatly, so the eruption differs in a like degree from a transient erythema lasting from twelve to twenty-four hours to a brilliant efflorescence lasting three or four days.

Plate XXXII gives a very good idea of the eruption of scarlet fever of a not very severe type. The frequent herpetic eruption near the commissures of the lip is well shown. The mouth pallor can also be seen.

Delayed rashes sometimes occur; that is to say, a patient will have the angina of scarlet fever, and six, seven, and in some instances ten, days may elapse before the eruption appears. During this time the patient has a high temperature with marked throat symptoms and an exudate on the tonsils.

Desquamation.—This commences in severe cases in four or five days from the beginning of the attack. In mild cases ten to fifteen days and sometimes twenty days elapse before the process begins. It may be very profuse or very slight, depending upon the brilliancy of the eruption and the condition of the skin. Large scales of epidermis 1 to 2 centimeters square may be exfoliated. Children, as a rule, do not desquamate to such an extent as adults, because the skin is much more pliable and soft than in the latter. This is notable in the hands and feet. Every case of scarlet fever does not desquamate. This is particularly true of the extremely mild attacks. The desquamation has been described as lamellar, in distinction from that of measles, which is furfuraceous; but this is arbitrary, as a severe attack of measles may be followed by a lamellar desquamation, while that of a mild attack of scarlet fever may be furfuraceous. Desquamation commences, as a rule, on the neck, in the axillæ and inguinal regions. Previous to this if the fingers are carefully examined there will be found a white line at the junction of the pulp of the finger with the nail, looking very much as if a fine superficial incision had been made. This cannot be seen unless a careful examination is made and the pulp of the finger is pulled away from the nail. This, of course, is commencing desquamation, but it can be seen before there is much, if any, general desquamation. This is often of great assistance in making a diagnosis after the disappearance of the eruption and before general desquamation is apparent. Many outbreaks of scarlet fever have been traced to their source by appreciation of the significance of the condition just described. In adults this separation of the epidermis of the fingers is much more pronounced than in children, but it can always be demonstrated in the very young. In some instances the epidermis of the palms and of the soles separates in one large piece. Sometimes the process of desquamation leaves the skin extremely sensitive to heat and cold, and for this reason great care should be exercised in applying hot applications and embrocations to the skin of a patient in the desquamative stage.

The process of primary desquamation is generally completed in five or six weeks; in rare instances eight weeks may elapse before the skin is in its normal condition. Secondary desquamation, by which is meant that exfoliation of the skin that sometimes, but not very frequently,

occurs after the true desquamation is over, is ended in about ten weeks. The feet are the last portions of the body to desquamate.

It is probable that the scarlet fever virus has a special action on the epidermis, as desquamation is usually more marked after a scarlet fever erythema than after other erythemas of similar intensity and duration. The amount is extremely variable, and although after the acute features have disappeared in uncomplicated cases, it is the only evidence of the disease, it cannot be depended on very much for diagnosis. Some patients after mild attacks do not desquamate and desquamation may follow many irritations of the skin. *Erythema scarlatiniforme* is especially characterized by profuse desquamation often involving the nails and hair. In scarlet fever the hair may fall in severe cases but loss of the nails is very rare.

Fig. 35

Desquamation in scarlet fever.

Cervical adenitis is a very common symptom, and may appear early or be delayed until convalescence. In an analysis of 5000 cases of scarlet fever the cervical glands were enlarged in about 50 per cent. Suppuration took place in about 8 per cent.

Complications.— *Nephritis.*—Albuminuria is not uncommon during the febrile stage, but is overemphasized as a diagnostic sign. This is not associated with signs of kidney insufficiency and should be distinguished from true nephritis, which rarely occurs before the end of the first week. In a series of 1000 patients it was found that in about 28 per cent. no albumin was found; the slightest possible trace was found in 40 per cent.; a very slight trace in 4.5 per cent.; a slight trace in 10 per cent.; a trace in 7 per cent.; and a large trace in 3 per cent. If the amount of albumin was sufficiently large to be estimated by fractions of 1 per cent. it was observed that about 3 per cent. had

one-tenth of 1 per cent.; 4 per cent. had one-eighth; and 2 per cent. had one-fourth. There were 15 instances in this series in which the amount of albumin was one-half of 1 per cent. Six of these patients died. A small amount of albumin, especially if a large quantity of urine is passed, does not necessarily indicate that the patient may not have a uremic convulsion. A patient may seem to be progressing favorably, passing a sufficient amount of urine with only a trace of albumin, when suddenly he has a convulsion and dies in a short time. In 5000 cases, 20 instances of this nature have occurred, three or four weeks after the commencement of not very severe attacks. Kidney complications may occur as late as six weeks after the onset. Chronic renal disease is not infrequently caused by scarlet fever, and the possibility of this should always be kept in mind. Nephritis is apparently due to a toxic scarlet fever substance, but streptococci cannot be excluded. The more severe the attack the more probability of kidney injury.

The signs are early diminution of the quantity of urine, œdema often very marked, pallor, albuminuria, and hematuria. Vomiting and fever not infrequently usher in the attack, but are not continued as a rule. The course is usually favorable under treatment, the acute symptoms disappearing in a few days or weeks. Albuminuria, cylindruria, and hematuria may persist for weeks, although the kidney work is properly performed, and finally clear. Anuria and mental dulness are very unfavorable in beginning nephritis. Uremia may occur with great suddenness even in patients apparently doing perfectly well.

In a large proportion the kidney appears to return to normal, although it may be more liable to subsequent injury. In a small number, chronic nephritis remains. The frequency of nephritis varies much in different epidermics and localities and with the management of the case.

Eyes.—The *eyes* are very rarely affected, although occasionally there may be slight conjunctivitis. A phlyctenular conjunctivitis or any chronic trouble is aggravated by an attack of scarlet fever. Slight or marked congestion of the conjunctiva, especially the palpebral, is present with the rash in most cases of moderate or marked scarlet fever.

Otitis Media.—This is one of the commonest complications and is responsible for many cases of deafness. Otitis may occur almost at the outset and at any time during the convalescence, but in the subsiding stage and early convalescence is most frequent. There may be intense pain or none at all. The aural discharge may be the first symptom unless the ears are repeatedly examined. Deafness is an early symptom; the drum is red, and soon bulging occurs, followed by perforation, with more or less sloughing of the membrane. The temperature is often high, but in some cases slight. In patients with fever from any cause, as septic throat, joints, etc., the ears may be easily overlooked. Adenoids and mouth-breathing are important predisposing factors and in patients with previously normal ears this complication is rare. Local sepsis of the throat or nose greatly increases the danger.

Mastoiditis may occur almost coincident with the otitis, but usually follows in days or weeks. Continued fever and profuse discharge are practically certain evidences of mastoid involvement; although resolution

may occur. Local tenderness and œdema over the mastoid indicate the need of immediate operation, and even in cases with prolonged discharge alone operation may be required. Bulging of the superior and lateral walls of the canal usually denotes mastoid involvement, but occurs with furunculosis of the external auditory canal. Lateral sinus thrombosis and brain abscess may occur if operation is delayed but are extremely rare when early operation is done. No patient with mastoiditis is too ill for operation, although in unfavorable cases simply opening the cells should be done and followed by a more thorough operation after the septic process in the throat has subsided. The percentage of otitis media in scarlet fever as given by different observers varies very considerably. Finlayson says that it was present in 10 per cent. of 4397 cases observed by him. Caiger found otitis media in 11 per cent. of 4015 cases of scarlet fever and Burchhart in 33 per cent. of his cases. At the South Department of the Boston City Hospital in 5000 cases 18 per cent. had middle ear trouble. When there are severe throat symptoms involvement of the middle ear may occur in 50 per cent. Cultures from the discharge in a comparatively small proportion showed the presence of the *Streptococcus pyogenes*. The most frequent organisms were the *Staphylococcus pyogenes, aureus,* and *citreus*.

Blood.—The blood has been carefully studied in reference to leukocytosis. Tileston and Locke[1] examined the blood in 35 cases of undoubted scarlet fever. Their conclusions are as follows:

1. "The blood of scarlatina in children differs from that in adults only in proportion to the differences in normal blood at the different ages.

2. "A slight secondary anemia is the rule in all but the very mild cases, varying directly with the severity and duration of the disease. The fall in hemoglobin is from 5 to 25 per cent. and in the erythrocytes from 100,000 to 700,000 per cmm. Both return to normal after a period of several weeks.

3. "A leukocytosis almost invariably accompanies the disease and runs a characteristic course. Rising abruptly on the second to eighth day (18,000 to 40,000 per cmm.) the count falls rapidly for a few days, then more gradually to reach normal, in convalescence, usually at the end of from three to six weeks.

4. "During the period of invasion and eruption the polynuclear leukocytes are both relatively and absolutely increased, but decrease gradually with the fall in the leukocytosis until convalescence, when they may become relatively, though never absolutely, below normal. The mononuclears take an exactly opposite course. With the onset the eosinophiles disappear entirely or are greatly reduced, to rise above normal when defervescence begins. This cosinophilia persists until late convalescence. Myelocytes are often seen in small numbers, as in all infectious diseases.

5. "Complications, with a few exceptions, exert no influence upon the course of the blood. If severe they may increase the anemia and in a

[1] *Journal of Infectious Diseases*, 1905, vol. ii, No. 3.

few instances (nephritis and diphtheria) even produce a rise in the leukocytosis."

Heart.—*Endocarditis* and *pericarditis* are special complications in scarlet fever. Two types are recognized: septic and simple or toxic, but the distinction is clinical and not clearly drawn. Septic endocarditis is rare and practically occurs only in severe attacks complicated with throat sepsis. It usually occurs early so that the common febrile lysis of scarlet fever is absent. Streptococci are the invariable cause and are present in the blood stream. Streptococcemia frequently occurs without endocarditis. There are usually murmurs and changes in the heart-sounds, but these may be absent or slight or obscured by rapid and noisy breathing. Delirium, stupor, restlessness, high fever, and loss of weight are present, and death invariably occurs so far as is known. Emboli may occur in the skin, lungs, and spleen.

Simple endocarditis may be due to toxins acting on the endothelium, but the trend of opinion is that there is a local infection with bacteria of less virulence than those causing the septic form. The time of occurrence is especially in the second and third week of the attack. Fever may occur at the outset but is not infrequently absent. A rising pulse rate is the commonest early sign, except murmurs. There is usually some dilatation with increase of the area of dulness. Endocarditis is very easily overlooked, and care should be taken to examine the heart frequently. Murmurs vary much in intensity and duration and as "functional murmurs" are common early differential diagnosis is not always possible.

Myocarditis is of little importance, and we have never known it alone to cause death. Irregularity may be present and at times extreme, but the outcome is good if endocarditis and pericarditis are absent. Myocardial signs are often marked in pericarditis.

Pericarditis is less frequent than endocarditis but is often obscure in signs and overlooked. When the rub is present it is easily recognized. Increase in the heart area and weakness of the muscle sounds are present. Recovery often is complete but great crippling may follow from adhesions.

In an analysis of 1000 cases a mitral systolic murmur was found in 187, gallop rhythm in 5, irregular action in 44, endocarditis in 3, and pericarditis in 5 cases. A large proportion of these murmurs were due to dilatation. In a second 1000 cases during an epidemic of a somewhat severe type, the writer found a mitral systolic murmur in 432, gallop rhythm in 15, irregularity in 100, endocarditis in 10, and pericarditis in 8 cases. In a third 1000 cases with a mild variety of disease, the figures were substantially the same as those in the first 1000 cases.

Lymphatic Glands.—The lymphatic glands, more particularly those of the neck, are enlarged to a greater or less extent in nearly every case. Sometimes this is so slight as to escape detection. In other cases the glands assume the size of a pigeon's egg, are extremely hard to the touch and not necessarily tender. In a third class, the glands are enormously enlarged; there is a sharp rise in temperature, marked tenderness exists, and finally the glands suppurate. This condition may appear early or thirty-five or forty days from the commencement of the attack.

Cellulitis.—Cellulitis of the neck and other parts in the severer types of the disease is not infrequent. In occasional cases the induration becomes so extensive that the whole neck presents a brawny red tender swelling, the so-called *Ludwig's angina*. This is apt to be attended by œdema of the glottis requiring tracheotomy. The process may extend to the mediastinum or develop into septicemia. After several incisions the œdema may go down, but the wounds slough and there may be fatal hemorrhage from ulceration of the vessels.

Hemorrhage.—There is some tendency to hemorrhage in scarlet fever and care must be taken in operations. The tendency to ecchymosis of the skin and at times of the mucous membranes has been noted. Fatal hemorrhage has been reported. We have had cases with fatal hemorrhage from the middle ear, from the neck, and from a wounded intercostal artery.

Phlebitis and *gangrene* are rare complications. The gangrene is usually dry and due to arterial thrombosis or embolism.

Meningitis occasionally occurs in the septic cases and is usually the result of infection through the ears or nose. It may be part of a septicemia. We have obtained pure cultures of streptococcus from the spinal fluid of septic cases in which meningeal signs were absent. In severe toxic cases meningeal symptoms may occur without meningitis.

Paronychia.—Paronychia is frequently observed, but, as a rule, it is a late symptom and does not occur until desquamation is thoroughly established. It is due to infection with the pus cocci.

Furuncles.—In a certain number of cases small boils form in various parts of the body and successive crops may appear.

Impetigo Contagiosa.—This is a not infrequent sequel. Sometimes the eruption may be so general as to be mistaken for varicella. During desquamation there are small abraded surfaces on the surface of the body which readily become infected with pus cocci from the finger nails.

Pneumonia.—This must always be considered in the severer types, although not very frequent. Bronchopneumonia occurs much more frequently than lobar pneumonia.

Pleuritis.—This frequently occurs, and *empyema* may appear as an early or late complication. The condition is grave and frequently the immediate cause of death. When streptococci are found in the pus the condition is critical in the extreme.

General Peritonitis.—General peritonitis due to streptococcus infection is extremely rare; that it may exist and not be recognized is possible, for the patient may be so delirious as to prevent a diagnosis being made, or the prostration may mask the characteristic symptoms and render a diagnosis impossible. Among 5000 cases of scarlet fever there have been a limited number with symptoms which suggested this complication, but the speedy subsidence of all symptoms and ultimate recovery would seem to prove that peritonitis could not have existed. In 4 out of 5000 cases peritonitis did actually occur; in these the attack of scarlet fever was not especially severe. This complication is exceedingly grave.

Arthritis.—Clinically there are two types, septic and the simple arthritis, although this separation, as in endocarditis, may possibly

be according to severity instead of essential differences in the infection. *Septic arthritis* is rare, usually in septic cases with ulceration of the throat. The large joints are usually involved but at times we have found the wrist and sternoclavicular affected. It is usually multiple and in one case eight joints were affected. The first symptom is usually pain or sensitiveness but so little may be complained of that unless the child's position is noted or the joints moved it may be overlooked. Soon swelling and fluid in the joints occur. Incision or aspiration shows a cloudy thin fluid containing a pure culture of streptococci, but if opened late the pus may be very thick. There are not infrequently periarticular pockets and the bursæ about the large joints may be affected either alone or with the joints. The arthritis is usually part of a septicemia and a fatal outcome is almost certain. Nephritis often occurs with it.

Scarlet Fever Arthritis.—This seems to be rather a specific form, occurring in early convalescence, characterized by moderate fever, tenderness, redness, heat, and swelling. It may attack the large joints but especially involves the fingers, wrist, and ankles and at times the knees. Free fluid in the joint may be present and in a few cases cultures have been negative. The process is benign, limited to a few days or a week, and leaves no deformity. It may be attended by endocarditis.

Jaundice.—This was observed in 15 of 5000 cases. It is not a symptom of any gravity and may occur at any time during the first three weeks.

Relapse.—It is the generally conceived idea that one attack of scarlet fever absolutely protects from a second; and while this may be true in a vast majority of cases, yet undoubted relapses do occur. This statement is made with the full understanding that the idea of an error in diagnosis must be combated. Second attacks of the disease occurring at intervals of two and three years or longer are not so uncommon. It is important to distinguish a true relapse from a pseudorelapse. A reinfection must also be differentiated from a relapse. A true relapse occurs in from thirty to thirty-five days after the disappearance of the eruption. The usual symptoms appear at the onset. A pseudorelapse, or a *reversio eruptionis,* takes place just after the disappearance of the rash; sometimes it may appear in ten or as late as fifteen days after the subsidence of all symptoms. A reinfection may take place about fifty days after the eruption has faded. The recurrence of the disease, as a rule, is not accompanied with any very violent symptoms. An attack of so-called tonsillitis which is frequently noticed in the convalescent scarlet fever wards may possibly be a mild reinfection, as the appearance of the throat in these cases is very similar to that in scarlet fever. In the 5000 cases of scarlet fever seen by the writer, relapses have occurred in 15 and second relapses in 5 cases. There have been 15 instances of reinfection occurring from forty to fifty days after the advent of the initial symptoms of the first attack. In 10 instances patients have been admitted with scarlet fever from two to four years after a first undoubted attack of the disease.

Diagnosis.—The diagnosis of a severe attack after the appearance of the eruption is not particularly difficult. In the preëruptive stage it is frequently extremely difficult and must be based upon the appear-

ance of the throat, the peculiar redness of which is to be distinguished from the appearance in diphtheria. In a good light, puncta can be seen in the roof of the mouth, but must be differentiated from those sometimes seen in health. The appearance of the puncta in the mouth is similar to that on the skin, but there is a difference in the color, the former being of a more brilliant red than the latter. In this stage the appearance of the tongue is of great assistance. The history of vomiting is also an aid, at this is one of the most constant symptoms. Convulsions are frequently present in young children, and rigors in adults. The onset of the attack, as a rule, is sudden, but there may be a feeling of malaise for two or three days previous to pronounced symptoms. A sudden rise in temperature and an attack of vomiting should give warning and place the physician on guard. This is of particular importance in diphtheria wards and in wards where non-infectious diseases are treated. The temperature is generally elevated, but a patient may have an attack of scarlet fever with a perfectly characteristic eruption and only a slight rise in temperature throughout the whole course.

A number of *special signs* have been brought forward during the past few years. Inclusion bodies in the polymorphonuclear leukocytes were noted by Döhle[1] and many reports have since appeared. These are present in practically every case of scarlet fever in the first few days, but are also present in many other diseases as diphtheria, sepsis, etc., being easily seen in the cytoplasm of the cells when thin blood smears are stained by Giemsa's stain, Wright or methylene blue, etc., as rounded oval or rod-like bodies chiefly at the periphery.

The *elbow line* noted by Pastia, is a brown coloration of the transverse folds of the axilla. It appears first as a wine red line or lines but soon becomes brown from decomposed blood cells. Similar lines may be seen in the groin and axilla but not so readily or frequently. The sign is practically invariably seen in the acute stage and early convalescence of scarlet fever but is also seen at times in measles and other erythemas, especially if there is a tendency to hemorrhage.

The *tourniquet sign*, Rumpel-Leede's sign, described by Leede, consists of the application of a constricting band as a Bier bandage, or the cuff of a sphygmomanometer, to the arm sufficiently tightly to cause a passive hyperemia without cutting off the arterial flow. In a few minutes to fifteen minutes numerous minute petechiæ appear at the fold of the elbow. This sign is also practically always present in scarlet fever, even for weeks in some cases, but occurs in other conditions with a tendency to hemorrhage. Schick drew attention to the fact that a slight pinching of the skin between the finger and thumb would cause a petechial spot. All these signs depend on the tendency of scarlet fever to produce petechiæ in the skin. Such petechiæ are nearly always seen at least in the severe cases in the elbow and axilla and groin.

The diagnosis of a mild attack is frequently very difficult, but a careful examination of the throat and an appreciation of the peculiar appearance of the tongue will in most instances be sufficient. There are cases in

[1] *Centralbl. f. Bact.*, November 23, 1911.

which the symptoms are so slight that it is impossible to decide definitely for or against the existence of scarlet fever. The only safe course is to isolate the patient for a certain length of time until he does or does not desquamate, although the absence of desquamation is not absolute proof that the patient has not had scarlet fever.

Measles.—This disease is sometimes mistaken for scarlet fever in the initial stage, but an examination for Koplik's sign and the coryza, with coughing and sneezing, ought to render this error extremely rare. In measles the blotchy rash is coarser, more widely separated, and occurs first on the face. When coalescent the rash may closely simulate the coalescent scarlatinal rash but usually on the shoulders or buttocks small irregular areas of normal skin will be found, and the mucous membrane signs allow a differentiation. There may be a marked rash on the soft palate but is usually larger and more blotchy than in scarlet fever. There is not the marked tendency for the mucous membrane inflammation to involve the fauces as in the angina of scarlet fever, but in some cases the inflammation is so extensive as to be confusing. Premonitory rashes must not be forgotten. Scarlet fever and measles are not infrequently associated and diagnosis is extremely difficult. It is impossible to state definitely regarding the nature of the disease until the patient has been under observation for twenty-four to forty-eight hours. In this disease Koplik's sign and the condition of the conjunctivæ are to be taken into account, together with the appearance of the tongue and the accentuation of the eruption in the axillæ and in the inguinal regions.

Rubella.—This disease, which very frequently serves as a cloak for either scarlet fever or measles, presents many difficulties. Sometimes the eruption is so fine as to resemble very closely that of scarlet fever. On the other hand, the small macules may simulate the commencing eruption of measles. There is absence of sore throat and usually coughing or sneezing occurs. The rash occurs first on the face extending rapidly over the body and is discrete and never attended by the diffuse blush which is so common in scarlet fever. Very early in the disease there may be found a marked fine red rash on the soft palate and at times the buccal mucous membranes. This is usually finer than measles and coarser than scarlet fever and is transient. Rubella is not nearly so common as is generally supposed, and many of the cases reported have been either scarlet fever or measles of a mild type. The glandular enlargement, on which so much stress is placed, is not of the slightest aid in differential diagnosis, as the same condition occurs in scarlet fever and measles. The writer has investigated a number of outbreaks of scarlet fever which were due to so-called attacks of rubella. In doubtful cases, it is vastly better to isolate the patient for a few days rather than run the risk of an error and thereby cause an outbreak of scarlet fever. Patients may have attacks of scarlet fever with very little constitutional disturbance, and this should influence the physician in making a diagnosis of scarlet fever in distinction from rubella.

Fourth Disease.—There has been a considerable amount of discussion during the past few years regarding a condition resembling scarlet fever to which this name has been given. While it is possible that there may

be such a disease, it is much more reasonable to suppose that the eruption described was, in fact, that of a mild attack of scarlet fever. From a somewhat extended experience in the diagnosis and treatment of the exanthemata, the writer can confidently state that, in his opinion, the existence of a "fourth disease" has not been proved, and that he has never seen just the condition which Dukes[1] described.

Among the 24,000 patients, the majority of whom were children, treated at the South Department of the Boston City Hospital during the past ten years, no such eruption as that described by Dr. Dukes has been observed. During this time there has been an immense number of anomalous eruptions not belonging to the exanthemata and also many anomalous types of the exanthemata, but no condition worthy of the name of "fourth disease" has been noticed. The writer cannot help feeling that, although the discussion regarding the "fourth disease" may possibly have done some good in causing the more careful examination of patients with eruptions and, consequently, a more accurate diagnosis, still on the other hand it has probably increased the prevalence of scarlet fever on account of incorrect diagnosis.

Erythema Infectiosum.—Escherich has described under this name an exanthem which may possibly be mistaken for scarlet fever, but the eruption is more macular than punctate, and the absence of throat symptoms and the appearance of the tongue ought to make the diagnosis comparatively easy. Stricker described in 1899 a disease probably the same as that described by Escherich. Tripker, in Coblenz, in 1901 described a similar disease. Plachte in 1904 also described this disease. Several other observers have also mentioned the existence of this exanthem. The writer has observed several cases of this nature. This disease is also frequently mistaken for measles, but in the cases that come under the observation of the writer, although the patients were not isolated, no cases of scarlet fever or of measles were contracted from them. That this disease is an entity cannot be disputed, and it is important from a diagnostic point of view, as all of the patients who had this eruption applied for admission to the scarlet fever wards or to the measles ward of the South Department. It is needless to say that they were refused admission. They were, however, carefully watched for some considerable time in order to verify the diagnosis. Desquamation to a limited extent was present in most of the cases, but it was not so general as in the case of scarlet fever. The absence of throat symptoms, the fact that the papillæ of the tongue were not enlarged, and the pronounced eruption on the face, were the principal points on which the diagnosis was based.

Lichen Tropicus.—This disease is frequently mistaken for scarlet fever, and when there is a rise in temperature, as not infrequently occurs in children, the diagnosis is somewhat difficult. If attention is paid to the condition of the throat, the peculiar appearance of the tongue, and to the fact that in scarlet fever the eruption is accentuated in the axillæ and in the groins, while in lichen tropicus it is not, a correct diagnosis can be made.

[1] *Lancet*, July 14, 1900.

Drug Eruptions.—Many drugs cause the appearance of a punctate erythema which it is frequently very difficult to differentiate from that of scarlet fever if the diagnosis is to be made simply from the condition of the skin. In all of these the diagnosis must be based upon the condition of the mucous membrane of the throat and on the appearance of the papillæ of the tongue, together with the constitutional disturbance.

Quinine in certain individuals will cause a very general eruption, punctate in character, which simulates that of scarlet fever to a remarkable degree. There is, however, no congestion of the throat and no enlargement of the papillæ of the tongue. Profuse desquamation follows this eruption which can in no way be distinguished from that of scarlet fever. It is lamellar in character, and frequently large scales of epidermis will be exfoliated from the palms and soles. In malarial fever after the chill, during the remission when quinine is administered, this eruption not infrequently occurs. At this time the condition of the mucous membrane of the mouth is of the greatest help in arriving at correct conclusions.

Strychnine in small doses sometimes, although rarely, causes a punctate erythema resembling that of scarlet fever.

Atropine causes an eruption which, from its resemblance to that of scarlet fever, caused the idea to be prevalent a few years ago that this drug was of advantage in the treatment of the disease. The dilatation of the pupils, the dryness of the fauces, the peculiar blush on the face, are the important points on which to base the differential diagnosis. It is remarkable how small an amount of atropine will sometimes cause an eruption.

Corrosive sublimate, when used for sterilization for an operation, will sometimes cause a punctate erythema twenty-four hours after its application. The constitutional disturbance following the operation and the nausea and vomiting caused by the ether render the diagnosis more difficult. In this condition the mucous membrane of the mouth is the only guide to a correct diagnosis.

Iodoform, even in very small quantities, may cause an eruption similar to that of scarlet fever. From the eruption alone a diagnosis is impossible; the determining factor is the mucous membrane of the mouth.

The eruption caused by *copaiba,* although more frequently resembling that of measles, may sometimes have a punctate appearance.

Premonitory Rashes.—In measles, smallpox, and varicella especially a scarlatiniform rash may occur with or precede the eruption. This has a tendency to be irregular in distribution and to lack uniformity, but it may absolutely simulate scarlet fever erythema. In these cases the signs of the other disease and the absence of the mucous membrane and tongue lesions of scarlet fever are of value. It must be recalled that two or more of these diseases may be associated.

In short, in making a diagnosis of scarlet fever the whole clinical picture must be taken into account, but the chief reliance must be placed on the condition of the mucous membrane of the mouth. The history of exposure is always a weak staff on which to lean, and probably has caused many errors of diagnosis.

"Surgical Scarlet Fever."—The existence of this in distinction from medical scarlet fever is a disputed point, but we are of the opinion that there is no such disease. Patients on whom a surgical operation has been performed, if exposed to scarlet fever, are no doubt more likely to contract the disease because the operation diminishes their resisting powers, but this does not constitute a distinct form of scarlet fever. Before the days of aseptic surgery, when septic rashes were more common, much more was heard regarding surgical scarlet fever.

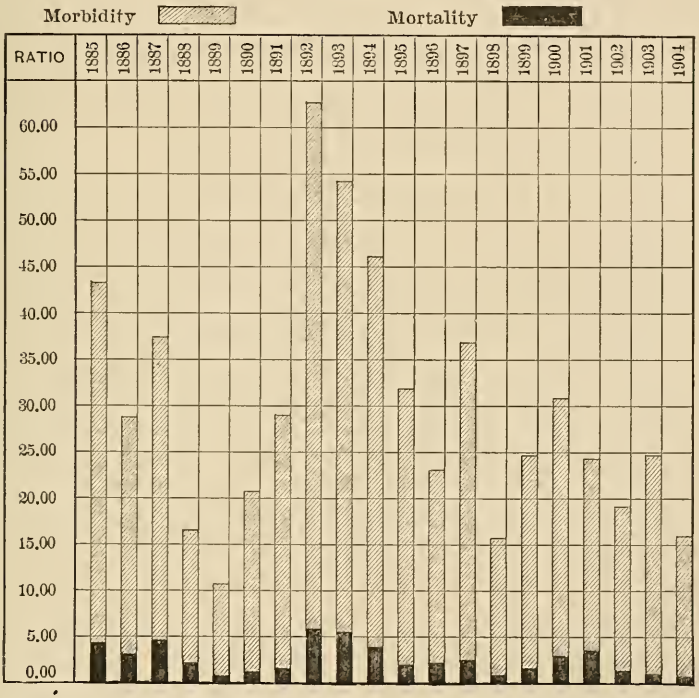
Patients who have burns of either the first or second degree, if exposed to scarlet fever, may contract the disease more readily than if the skin is intact, but this is not surgical scarlet fever; it is scarlet fever in the wounded. Considering the great frequency of burns and the prevalence of scarlet fever, it is remarkable that scarlet fever is not more often contracted by children with burns. An individual who has had repeated attacks of appendicitis may have the inflammation excited in that situation by the initial symptoms of scarlet fever. The nausea and vomiting attendant on the onset of the disease may lead the surgeon to decide on an operation. Twenty-four or forty-eight hours later an eruption of scarlet fever appears. This is not surgical scarlet fever but scarlet fever in the wounded. Several such instances have been observed by the writer. In these cases investigation proved that there had been a direct exposure to scarlet fever a short time previous to the operation. We have known nurses to develop scarlet fever a few days after pricks of the fingers, paronychias, etc., and in a physician scarlet fever occurred three days after an autopsy wound on a scarlet fever case. There is no way by which we may exclude the contraction of the disease in these cases in the usual way.

Prophylaxis.—The segregation for a long time of patients ill with scarlet fever is the only method of preventing the prevalence of the disease. We must depend upon isolation, preferably in special hospitals. In a tenement house it is very difficult and well-nigh impossible to properly isolate a patient. The medical inspection of schools, if properly conducted, would be an efficient means of limiting scarlet fever. It is an undeniable fact that walking cases are responsible for many outbreaks. As scarlet fever is infectious from the initial vomiting often for several weeks, it is evident that isolation should be early and continue for a long time. It has been stated by some observers that scarlet fever cannot be communicated before the appearance of the eruption, but this is not correct, as a child may communicate scarlet fever during the initial stage of vomiting and sore throat.

Discharges from the nose and from the ears of a convalescent scarlet fever patient are undoubtedly infectious. It therefore follows that in order to accomplish anything in limiting the spread of scarlet fever isolation must be early, rigidly enforced, and continued for a long time. As the poison of scarlet fever remains active for a long time and can be conveyed by fomites, it is very important that the clothing worn by the patient at the time he was taken ill should be thoroughly disinfected. It is necessary to be absolutely sure that disinfection is effectual, and in order to accomplish this the details must be carefully carried out.

Isolation hospitals are the most effectual means for diminishing the spread of infectious diseases in crowded cities. Glasgow has probably suffered more in this respect than any other city, and it was not until a special hospital for the treatment of these diseases was established that there was any marked diminution either in the mortality or morbidity of scarlet fever. Previous to 1888 in Boston there was no special provision for the care of patients ill with scarlet fever, and in 1887 it was decided by the Trustees of the Boston City Hospital to erect a pavilion for this purpose. At first there were comparatively few applications for admission, but as time went on the public generally began to

Fig. 36



Ratio of morbidity and ratio of mortality of scarlet fever in Boston per 10,000 of the population from 1885 to 1904 inclusive.

realize the advantage of sending patients to the hospital. After a time this ward became crowded, so that many applicants were refused admission. In 1892 it was decided to erect a large hospital for infectious diseases, particularly scarlet fever and diphtheria, which was opened in 1895. The effect on the morbidity ratio and mortality ratio of scarlet fever since the establishment of this hospital is shown in Fig. 36. It will be seen that since 1895 the prevalence of the disease has diminished to a very considerable extent and that the mortality ratio has also diminished. The average ratio of morbidity of scarlet fever from 1885 to 1894 was 34.84, while that from 1895 to 1904 was 24.68—a very considerable

diminution. The mortality rate for the first period was 2.99, while that for the second period was 1.91. A large proportion of the patients in Boston who are seriously ill with scarlet fever are sent to the hospital, but those who have the milder attacks are not isolated and therefore serve as potent factors in causing its spread.

The length of time that a patient ill with scarlet fever should be isolated has been the subject of careful study. The practice in different countries varies very considerably, as, for instance, in Glasgow the time is much longer than in England and in this country. It is not improbable that some patients cease to be contagious in a very few weeks and it is unquestionable that contagion may persist in a case for weeks (20 at least) when there are mucous membrane lesions. In the absence of proof of when contagiousness ceases in any case, it is wise to insist on a minimum period of at least five weeks, and to prolong this indefinitely if lesions of the mucous membranes are present. While discharges from sinuses are contagious there is much less danger, because they are covered with a dressing and are not liable to spread the infection on the patient's fingers as occurs in nasal discharges.

"*Return Cases.*"—The occurrence of another case in a family following release of a patient from isolation is unfortunate but not entirely preventable. We have known many cases where an ear has discharged again after a period of complete dryness, or where an acute rhinitis has occurred days or weeks after discharge from the hospital, and other cases resulted from contact. At the South Department the average length of time that a patient remains in the hospital is fifty days. No patient who has a discharge from the nose or an abnormal condition of the throat leaves the hospital. Of 3000 patients discharged from the scarlet fever wards, there was a percentage of 1.74 of alleged return cases. Investigation failed to show anything abnormal in the condition of the individuals who were supposed to be the cause of the alleged return cases.

In 1898 the Metropolitan Asylums Board of London conducted a series of investigations (by Simpson[1]). The conclusions reached were as follows:

"The committee are impressed with the small percentage of those cases which, on investigation, were found to give rise to fresh infection, viz., 1.1 per cent. of the total cases discharged from hospital of diphtheria and scarlet fever taken together. They also note that of these no fewer than 80 per cent. were suffering from some mucous discharge, either during their stay in hospital or shortly subsequent to their return home.

"The total number of return cases of scarlet fever was 90, giving a percentage of 1.3 of the total number discharged. In endeavoring to arrive at a definite conclusion as to the necessary length of detention in scarlet fever, there are two points on which elucidation is required, the degree of infectivity attaching to (*a*) the desquamation of the skin and (*b*) any mucous discharge occurring during convalescence.

"In respect of the infectivity of the later desquamation of the skin in scarlet fever, it is to be observed in Dr. Simpson's investigation that in

[1] Metropolitan Asylums Board—London, *Annual Report*, 1903.

only 2.7 per cent. was there any reason to suspect desquamation of the skin as the cause of secondary infection. The relatively high degree of infectivity of the mucous discharges, as compared with the later desquamation of the skin in scarlet fever, as shown in the report, is one which is obtaining an increasing support among those of the profession who have had much to do with infectious diseases. It would suggest that possibly too much importance has been hitherto attached to the infectivity of the skin during the later weeks of scarlatinal convalescence."

In many instances the alleged return cases have no connection with the discharged patient. It is not an infrequent occurrence for a child to be admitted to the scarlet fever wards a few hours before his brother or sister is discharged. If these discharged patients had arrived at their homes twenty-four or forty-eight hours earlier, as in many instances they would, if the parents had come for them as soon as notified, the second cases would have been considered return cases. It is also a significant fact that in the majority of the return cases the patients are of the school age and, therefore, the possiblity of infection other than that of the patient who has been discharged is very great. That the clothing worn by the patient when he was taken ill and which was packed away during the stay in hospital may be a source of infection is extremely probable.

Vaccination Against Scarlet Fever with the Streptococcus. Most of the work on this subject has been done by Russians led by Gabritschewsky (1906). The results were rather striking; in different villages the vaccinated persons contracted scarlet fever in from 0 to 8.3 per cent. as contrasted with from 13.3 to 70.6 per cent. incidence in the unvaccinated. The disease was milder and the mortality lower in the vaccinated cases and complications were rare and mild. Of 91 unvaccinated children observed by Smirnoff[1] 37.3 per cent. developed scarlet fever and of 127 vaccinated children 3.93 per cent. The protection by repeated injections is shown by the table:

	Cases.	Incidence. Per cent.
Vaccinated once	1295	1.69
Vaccinated twice	1018	0.19
Vaccinated thrice	256	0.00

The streptococci as used by Gabritschewsky were grown in boullion, killed by heat at 60° C. with 0.5 per cent. carbolic added. Each cc. equalled 0.02 to 0.03 gram of sediment. The dose was from 0.25 to 1 cc. subcutaneously. Watters (1912) reported the use of vaccine in 100,000,000 to 500,000,000 doses in the immunization of nurses. Of the vaccinated 2.7 per cent. contracted scarlet fever and 35.4 per cent. of the unvaccinated. His series was small and the incidence of 35.4 per cent. in the unvaccinated is unusually high. Although the figures are very suggestive more extended experience is required to demonstrate the value of vaccine as a prophylactic because of the great natural variation in the incidence and severity of scarlet fever.

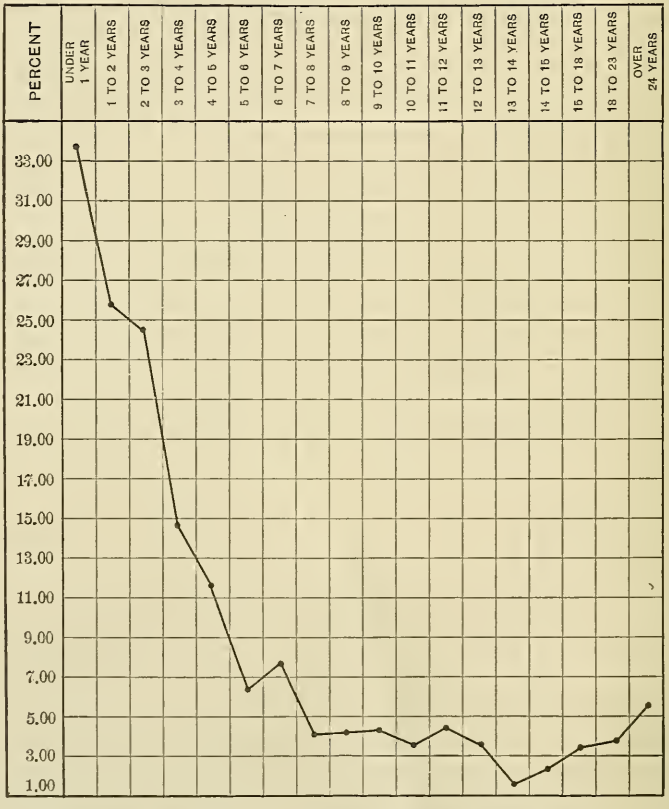
Prognosis.—This depends very considerably on the complications and not on the disease itself, except in the fulminating type. In a

[1] *Vrach. Gaz.*, 1909, xv, 368.

moderately severe attack, provided there are no complications, the prognosis is favorable. It is remarkable how seriously ill a patient may be for four or five days and how rapidly at the end of this time he will commence to improve. On the other hand, a patient with an apparently mild attack, if there are complications, may succumb suddenly. The physician should always have in mind the possibility of nephritis, the dangers of endocarditis and pericarditis, the chances of a bronchopneumonia, the possible occurrence of an empyema or mastoiditis; it is therefore wise to give a guarded prognosis in every case.

Meningitis occurs very rarely, as autopsies have shown, but a condition suggestive of meningitis does not infrequently occur. This is exceedingly serious and should always suggest an unfavorable prognosis. Few patients with meningitic symptoms recover.

FIG. 37



The percentage of mortality by age in 5000 cases of scarlet fever.

Uremic convulsions are always a cause for apprehension. About 50 per cent. of patients in this condition succumb.

Empyema is a very serious complication. Only a small proportion recover, and in those who do convalescence is extremely tedious. Bron-

chopneumonia and, in a certain number of cases, lobar pneumonia are responsible for about 22 per cent. of deaths; it therefore follows that lung complications are of great significance.

Endocarditis and pericarditis of the septic type attended by high fever mean death. Simple endocarditis and pericarditis may entirely resolve but more often lead to more or less crippling of the heart; practically never to death directly.

Mastoiditis, if not relieved by an early operation, may cause death by extension of the inflammation to the brain.

Age is an important factor in influencing the prognosis. The percentage of mortality in very young children is high (Fig. 37). It will be seen that under one year of age the mortality was 33 per cent. and from five to six years of age it was only 6 per cent. The lowest rate, 1 per cent., occurred in patients from thirteen to fourteen years of age.

Scarlet fever occurring in the course of acute diseases and in patients on whom a surgical operation has been performed is sufficient reason for a grave prognosis. A woman in the puerperal state, if she contracts scarlet fever, is always in a serious condition.

As epidemics vary in severity no definite rules can be given regarding prognosis. Each case must be judged on its merits. The mortality varies in different epidemics from 4 to 15 with an average of 8.42 per cent. This rate is estimated on 37,810 cases in Boston during the past twenty-eight years. Johannsen gives the mortality in Norway in 84,580 cases as 14.17 per cent. Caiger gives the mortality of 81,350 cases treated in the hospitals of the Metropolitan Asylums Board of London as 8 per cent. The death-rate in the Municipal Hospital of Philadelphia from 1891 to 1902 in 5213 cases was 9.72 per cent. At the South Department of the Boston City Hospital the death-rate in 5000 cases was 9.28 per cent.

Treatment.—This is both hygienic and medical. The *hygienic* treatment is simple. It consists in placing the patient in a well-ventilated apartment from which all hangings and upholstered furniture have been removed. Isolation, on which too much stress cannot be placed, must be rigid. Only two persons should have the immediate care of the patient,—the day nurse and the night nurse. The physician when making his visits should wear a gown and a cap. After the visit he should be careful to wash his face and hands in a solution of corrosive sublimate. The nurses should be careful to change their clothing when they leave the patient and come in contact with other persons. The room should not be overheated; the temperature should never exceed 65° F. in cold weather. In warm weather it is frequently impossible to keep the temperature at this point. The diet should be bland; milk and cereals for the first two or three weeks of the illness is the most desirable article. The patient, if there is no nausea, should be induced to drink a large amount of water. Cracked ice and ice-cream, particularly if the anginose symptoms are pronounced, are frequently very grateful. The bedclothing should be light, as there is nothing that contributes so much to discomfort as heavy coverings. There is very little danger of contracting a cold during an attack of scarlet fever. The popular

idea that by causing perspiration the eruption will become more brilliant is incorrect. Recession of the eruption, although it sometimes occurs, is not caused by cold, but is a part of the natural history of the disease. With a failing circulation, from a weak heat, vasomotor paralysis, etc., the rash may disappear—the much dreaded "striking in" of the rash.

The *medical* treatment must be symptomatic. The different phases of the disease must be carefully watched and untoward symptoms alleviated by the proper remedies. There is no drug that has a specific action. In the mild cases no medication is required. If there is marked prostration, alcohol can be administered in large doses but routine treatment by alcoholic stimulation is to be reprobated. Strychnine is a good stimulant in certain cases and children, as a rule, bear it very well.

If there is marked delirium, morphine in small doses, according to the age of the patient, can be used with marked benefit. It must be borne in mind that children do not bear morphine well, and it should be administered with the utmost caution.

The bowels should be kept open by mild laxatives. Compound licorice powder is a very good preparation. Calomel in small and divided doses is often of advantage. Irritant diuretics should never be used, as the kidneys are always congested to a greater or less extent. The less that is done in the direct treatment of the kidneys by diuretics the better. The patient should have large amounts of water. Flaxseed tea will sometimes be more agreeable than water. Orange-flower water is a good preparation. Barley-water may also be taken. Weak cream of tartar water is frequently very grateful.

If there is swelling of the cervical glands, ice-collars are frequently of marked benefit, but they must not be contined for too long a time. As soon as there is a suspicion of fluctuation, incision should be made. Poultices are of doubtful advantage previous to incision and of no use after the pus has been evacuated. In the treatment of cervical adenitis, while it is important to have a sufficiently large opening for proper drainage, it is well to bear in mind that an unnecessarily long incision causes an unsightly scar.

Digitalis, if there is no dilatation of the heart and its action is weak, may be administered with satisfactory results, but it should be given with the utmost care, as in certain cases it may do harm.

Hydrotherapy reduces the temperature and calms the delirium. When the temperature is above 103° F. sponging with water at a temperature of 85° F. is frequently of great use. Immersion in a bath-tub with the water at 85° F. may also be used. Children, as a rule, however, bear sponging better than baths. If the patient bears sponging well, and if the temperature is reduced two or three degrees by it, the prognosis is favorable; if, however, the sponging causes a chill, and the temperature is not reduced, it is better to omit it. An ice-cap should always be placed on the head of the patient during the sponge bath. In patients with a full, strong, bounding pulse and an active delirium the fan bath is often of great use; the patient is wrapped in one layer of gauze and the body is then sprinkled with water at a temperature of about 90° F. A nurse stands on each side of the patient and fans him vigorously for

ten or fifteen minutes. The fanning causes the rapid evaporation of the water and the temperature is reduced in a marked degree. The ice-cap should always be applied in these cases. The pulse should be carefully watched. In some instances the water may be of a lower temperature. While sponging and the tub bath are of undoubted advantage in many cases, there are instances in which this treatment does not seem to be beneficial. A cold water pack can be administered, and frequently is more beneficial than the sponge or tub bath.

Inunction with cold cream or cocoa butter will sometimes reduce the temperature to a certain extent. Vaseline is not adapted for this purpose and cocoa butter is the best agent to use. The addition of carbolic acid to the substances used for inunction does not do any good, and when we take into account the actively absorbent condition of the skin in scarlet fever it may cause poisoning. Cases are on record where a very small amount of carbolic acid in cold cream used for inunction has been followed by very serious symptoms.

FIG. 38

Noma in scarlet fever.

Placing the patient in a cold room at a temperature of 58° F. with very little bedclothing has been advised. The writer has seen satisfactory results from this method of treatment, but it cannot be recommended as routine practice. Antipyretics are of doubtful advantage. In an adult with a full, bounding pulse and a high temperature, phenacetine may be of benefit, but must be administered with care. In children it is to be absolutely prohibited. Quinine in large doses is of no benefit.

Throat.—If the attack is complicated by diphtheria, antitoxin should always be administered in substantial doses. There is no danger of causing trouble with the kidneys by the use of the serum. If the anginose

symptoms are comparatively mild, irrigating the throat with a weak Dobell's solution or a solution of boric acid contributes to the comfort. Children will not use gargles and sprays frighten them. When the anginose symptoms are pronounced, spraying the throat with diluted peroxide of hydrogen, if it can be accomplished without too much resistance on the part of the patient, may be advised. Direct applications to the throat by a swab saturated with Loeffler's iron toluol solution is of benefit. The swab should be held in contact with the diseased parts for a short time. Irrigation of the throat with a solution of corrosive sublimate, 1 to 8000, or with a solution of permanganate of potash, 1 to 2000, can be used. When there are small gangrenous patches in the throat, tincture of iodine may be applied.

Noma.—Noma occurs rarely in the course of scarlet fever, but is a complication of very great severity. Curetting and the application of fuming nitric acid may be of use or, better, the cautery. If the process extends, excision may be tried, but the possibility of its doing any good is very slight. Careful attention to the mouth and teeth do much to prevent this complication. Washing out the mouth frequently with mild alkaline solutions, removal of tartar and old loose teeth and carious roots, and prompt treatment of ulcers at the gum margin with hydrogen peroxide swabs followed by 2 per cent. chromic acid solution applications once or twice daily lessen the chance of noma.

Purulent Rhinitis.—If there is a profuse discharge from the nose, cleansing with swabs of absorbent cotton and the insufflation of calomel are the best methods of treatment. Irrigation of the nose, on account of the danger of causing middle-ear disease, cannot be too strongly deprecated. Albolene dropped in the nose at short intervals helps. It may be medicated to advantage by the addition of 1 to 2 grains of iodine, or 2 to 10 grains of menthol and camphor and eucalyptol. Albolene may be used in the dry, foul mouth when the nose is obstructed and mouth-breathing occurs. Ammoniated mercury ointment is a good application to the nose.

Arthritis is self-limited and is benefited by rest. Splints are rarely needed, but supporting bandages of cotton with oil of gaultheria and cotton-seed oil in equal parts and sheet wadding often give relief.

Salicylates should be avoided because of kidney irritation, and if given should be administered with sodium bicarbonate.

In septic arthritis early operation, irrigation, rest, immobilization, and prevention of deformities are indicated.

Endocarditis and Pericarditis.—Rest in bed is the most important factor in treatment and should be carried out for months. There is no important lowering of the blood pressure in scarlet fever, and stimulants should not be given.

Ears.—These should receive careful attention during the whole course. It is not sufficient to wait for the development of symptoms, but the ears should be carefully examined every two or three days to see if there is anything abnormal in the appearance of the membrane.

G. A. Leland describes three varieties of middle-ear disease in scarlet fever, and gives the following directions for incision of the drum-head:

"First, the regular sthenic variety, in which the drum-head is red, somewhat thickened, with the luster abolished and the contiguous canal of the same appearance. This is accompanied by extreme pain; the onset is sudden and the bulging occurs early. Incision of the drum-head should be very free, beginning in the lower inferior quadrant, midway between the umbo and the posterior wall, extending upward three-quarters of the distance to the posterior fold and then backward to come out on the external canal.

"Second, there is a variety which is not characterized by pain, especially in children and where the only warning that the ears are affected is a rise in temperature. The examination of the ears will reveal a drum-head which may or may not be bulging, but which has a macerated look. It is thickened, lusterless, the landmarks can only be faintly distinguished, the light reflex is absent, and there is only a slight redness of the contiguous wall of the bony canal. If perforation has not taken place a free incision should be made for the sake of drainage not only of the tympanic cavity but for local depletion of the membrane itself, and also, which is to be considered a very important point, to insure that the perforation shall be at the point of election, namely, the posterior inferior quadrant. Although this variety of drum-head may be pathologically perforated without suffering, it is the better practice to incise it in order to limit destruction as much as possible.

"Third, this variety of middle-ear disease is subacute, the drum-head is more or less transparent and pinkish in color. The tympanic plexus of vessels are very markedly filled, streaking down over the membrana flaccida into the swollen postmanubrial vessels. There is more or less effusion present in the cavity. This condition frequently occurs without pain in children, and in adults with only a transient earache. There is always a slight rise in temperature.

"Incision of the drum-head may be described as follows: Special attention being drawn to antisepsis, the avoidance of unnecessary destruction and to the after care, the auricle and contiguous skin of the scalp and face should be thoroughly washed. The external canal should be thorougly washed by cotton on an applicator, and a solution of corrosive sublimate, 1 to 1000, which may be allowed to remain in the canal for fifteen or twenty minutes and then removed with sterile wicks. Then with a spear-shaped paracentesis needle, or a slightly curved bistoury previously soaked in a saturated solution of boracic acid in alcohol and allowed to dry, which materially assists the vision in the introduction of the sterilized blade into the small external canal, the puncture should be made in the lower part of the posterior segment of the drum-head, which is almost without exception the most prominent part, and carried through the membrane only.

"In the third variety just mentioned a small cut through the lower two-thirds of the posterior half of the drum-head will be sufficient. In the other two varieties a large incision is indicated. After introducing the point of the instrument it should be carried upward and outward two-thirds of the extent of the membrana tympani and then backward to the posterior wall, care being taken to withdraw the point outward

far enough to avoid the incudostapedial joint and yet to completely divide the membrane itself.

"The treatment after incision should be carried out with strict attention to surgical cleanliness, and to this end a wick of sterile or corrosive sublimate cotton is introduced gently into the canal to assist the exit of the discharge by capillary attraction. On the outside of the wick a pad of the same cotton should be placed and changed as soon as it becomes wet, the wick being changed once or twice in twenty-four hours according to the amount of the discharge. Instillation of corrosive sublimate, one part to three or four thousand, may be made to sterilize the external canal and render it less liable to secondary infection, which, in the form of localized furunculosis, may give the patient considerable suffering. As long as the discharge continues free the incision requires no attention, but if the discharge diminishes or stops and there is a rise in temperature and pain a second incision should be made."

If there is pain and tenderness in the mastoid region, the Leiter coil or the Sprague ear ice-bag should be applied. If there is not relief at the end of forty-eight hours this treatment should be omitted. The continued use of the ice-bag will mask the symptoms so that a dangerous condition may supervene without proper warning. An early operation is to be advised in inflammation of the mastoid cells. The condition of the patient is rendered hazardous by waiting until there is marked swelling behind the ear and a great amount of tenderness. A long-continued profuse discharge from the meatus without any tenderness behind the ear is an indication for the mastoid operation not only for the relief of this symptom but in order that the hearing may be saved.

The choice of the operation must be made in each individual case, based on the condition of the patient. An early operation has been advised in each case occurring at the South Department of the Boston City Hospital and the results have been satisfactory, no death having occurred in sixty operations.

Nephritis.—Absolute rest in bed is imperative; the diet should be restricted, the bowels receive attention, and warm baths given. Allusion has been made to the importance of forcing liquids as a part of the routine treatment. Fomentations over the region of the kidneys are frequently of benefit. When there are twitchings of the muscles, delirium and stupor, a hot pack or a warm bath should be given. A warm bath is perhaps more satisfactory. Vapor baths are of advantage, but the hot air bath very rarely does any good. The pack can be given in the following way: The patient is wrapped in a blanket which has been wrung out of water at a temperature of 100° F. A dry blanket is placed over this and then the patient is covered with rubber cloth. The patient should have an ice-cap applied during the time that he is in the pack. It must be borne in mind that the skin of a patient ill with scarlet fever is extremely sensitive to heat, and therefore care must be exercised not to have the temperature of the water above 100° F. If convulsions supervene, resort must be had to ether carefully administered. Pilocarpine is of doubtful advantage and should rarely be given to children. Nitroglycerin in rare instances, in doses of gr. $\frac{1}{300}$, may sometimes be of use.

A saline infusion is frequently followed by a relief of the symptoms. The intravenous injection of salt solution has sometimes been followed by satisfactory results. Venesection has been advised previous to the intravenous injection. It is doubtful how much good hydrate of chloral, by the mouth or by the rectum, has accomplished in the convulsive seizure. The writer has not seen any advantage from its use in children. Morphine in small doses hypodermically may control the convulsive movements, but it has no effect on the condition of the kidneys. If there is suppression of urine, if the quantity is diminished to a considerable extent, even if there are no convulsive movements, the hot pack and the injection of the normal salt solution should be immediately resorted to. It is better to ward off the convulsions by the method of treatment just described than to wait until the more pronounced symptoms of uremia are in evidence. Much can be done to prevent or minimize the danger of nephritis. Following the belief that it is the result of toxic action on the kidneys, our efforts in the acute stage, in the absence of any specific, should be to aid in rapid exchange of fluid in the body by free administration of water and thus dilute the toxin. Elimination by other channels than the kidney should be secured, so far as possible, by the bowels, lungs, and skin. Hot daily bathing has been of great advantage. Irritant cathartics should be avoided. The further application of the principles of kidney rest as developed by von Noorden is essential. This means *rest in bed*, for three to five weeks, even temperature of the body and avoidance of loss of heat, avoidance of chilling of the skin, and a *diet* free from irritants, low in proteins, with no nucleoproteins or extractives, and containing sufficient carbohydrates and fat for caloric needs. Fat is not well tolerated in large amounts. Complete exclusion of protein has seemed to us inadvisable as the breaking down of the body tissues may be rapid in scarlet fever. The limitation of proteins is of extreme importance; about 0.5 gram. per kilo of the patient's weight should be given per day the first few weeks. Broths should be avoided and spices not used. Milk solely is not a good diet, but answers the purpose very well as a basis, the amount being given to secure the amount of protein desired and sugars and other carbohydrates added to the desired amount. This protective treatment should be carried on for at least three weeks. During the past five years the application of these principles in our wards has been attended by markedly good results. Only two deaths in nephritis cases occurred, one of which was a case of septicemia and septic arthritis and the other a case of pneumonia and empyema. No patient has had uremia except the one with empyema, who had convulsions preceding the pneumonia. The occurrence of nephritis has been markedly reduced so that cases with anasarca are extremely rare. A small number have shown casts, blood cells, and albumin usually without clinical signs of kidney insufficiency. Only two cases of partial anuria have occurred. This has been in marked contrast to the cases entering with nephritis during the convalescence, in whom anasarca has often been marked, and blood and albumin very abundant in the urine, vomiting and headache pronounced, and five of whom have died with uremia. It is very striking in these cases

that proper kidney care was invariably absent. The after-treatment of nephritis consists of a careful regulation of the diet and work and the administration of iron.

Serumtherapy.—Escherich and Moser since 1902 have had remarkable results in the serum treatment of scarlet fever. The dose of the serum is quite large, being 200 cc., but no injurious results have been noticed. Shaw says that the mortality average in this hospital was 14.5 per cent. for four years before the serum treatment was adopted, and that since its use the mortality rate for four years was 8 per cent. Although it cannot be held that the streptococcus is the cause of scarlet fever, its unquestionable relation to the sepsis of the disease and its great influence on the mortality make such efforts logical. The use of ordinary antistreptococcus serum, in doses of 200 cc., has not been of striking benefit in our wards.

Jochmann and Michaelis (1910) found beneficial results from combined serum and vaccine treatment, although of 52 cases of severe type 26.9 per cent. died, the remainder recovered without complications. Egis and Langovoy (1907) had a marked reduction of mortality of from 47.4 to 16.1 per cent. in 400 cases but complications were not especially influenced. Schick (1912) reported favorable results with Moser's serum. He says it is best in toxic cases without septic throat and that complications are much reduced. The results in a disease so frequently ending by lysis and rapidly subsiding naturally are far from satisfactory as a proof of its curative value. This is especially suggested by the slight evidence of its prevention of streptococcus complications and that its value as noted by Schick was less in cases with the septic throat.

Large dosage of serum should be used in treatment, especially as there is at present no method of standardization; 200 to 400 cc. should be given as early as possible. The fact that it is harmless, of some benefit, and that it may contain suitable antibodies, at least in some if not all cases, make its use advisable in severe cases when it can be obtained. Serum from human convalescents has been used by Schwenkenbecker at Frankfort and by Reiss and Jungmann (1912). With doses of 40 to 100 cc. of mixed serum the temperature was rapidly reduced, but throat conditions and complications were practically unaltered.

Vaccine treatment has not as yet been demonstrated of value. Weaver (1911) did not find that vaccines had any influence in preventing the complications, but that there was a tendency to clear more rapidly. Kolmer and Weston (1911) had good results in the treatment of post-scarlatinal rhinitis and an effect in limiting the period of contagion.

Salvarsan.—The use of salvarsan was suggested by the discovery in work on the Wassermann reaction that a certain percentage of scarlet fever sera fixed complement, and by the belief that it might be a protozoön disease and thus possibly benefited by arsenic. Salvarsan has been used in a number of cases with apparently good results (Klemperer). The dosage intravenously was 0.1 to 0.2 gram for infants to 0.5 gram for adults.

CHAPTER XXVI

MEASLES—RUBELLA—THE FOURTH DISEASE—ERYTHEMA INFECTIOSUM—MUMPS

By JOHN RUHRÄH, M.D.

MEASLES

Definition.—Measles is a specific infectious disease characterized by extreme contagiousness, fever, catarrhal symptoms, both prodromal and during the height of the disease, a characteristic early eruption in the mouth—Koplik spots—and later by a characteristic enanthem, exanthem, and a branny desquamation during convalescence.

Etiology.—At present measles is the most widely spread infectious disease, as it is found over the entire world uninfluenced by climate or weather except that it is slightly more prevalent in cold weather, probably due to people being more crowded together and so giving greater opportunity for infection. The disease is always present in the larger cities, but from time to time epidemics of more or less virulence occur, and these are the result of increased virulence on the part of the disease or of lessened resistance on the part of the inhabitants or in some instances to a new set of children having grown up. From time to time measles occurs as a pandemic. *Susceptibility* is very great but seems to vary from time to time as individuals may be exposed in one or more epidemics and not contract the disease and then be infected by a subsequent exposure. As few persons escape infection altogether, we may assume that but very few are entirely immune.

Measles is transmitted by direct contact in nearly every instance. While it may be possible that the disease can be transmitted by a third person or by fomites, the time which elapses from the contact with the infected person must be short. We have at the present time no information whatever regarding measles "carriers." There seems to be little or no danger of contracting the disease from apartments previously occupied by measles patients, and there are numerous instances in which families with susceptible children have moved into rooms in which measles patients had been living and there was no infection. If two weeks have elapsed, rooms may be regarded as perfectly safe even if they have not been disinfected. The disease is most frequently transmitted through schools, and the child in the preëruptive stage can transmit the disease to an enormous number of others, which explains the outbreak of a large number of cases on nearly the same day. Childrens' parties are another frequent source of infection, and in hospitals and asylums outbreaks frequently follow the admission of a case of measles in the preëruptive stage.

The disease apparently can be carried a short distance through the air, and it is well-known how difficult it is to isolate measles patients unless a separate open air space intervenes. Instances have been reported where a child has taken measles from a patient on the other side of the ward after an exposure as short as half an hour, with no apparent means of the disease having been transmitted otherwise than through the air. In Grancher's wards, in Paris, where special studies were made to determine the transmissibility and the possibility of preventing its spread, it was found that the infection of measles could be reduced two-thirds but could not be prevented altogether. It would seem that the contagion varies in virulence, some epidemics being very widespread and others more or less limited under essentially the same conditions. The disease may be transmitted from the time of the first catarrhal symptoms, and possibly before, and until the disease reaches its height. The infectiousness is very marked early and is probably greatest about the time the eruption is coming out. When the eruption begins to fade the danger of transmission diminishes, and during the stage of desquamation the danger of transmitting the disease is slight, if there is any at all. Until we have some more definite knowledge concerning the infectiousness of measles, it is a good rule to allow at least three weeks from the onset to elapse before a child mingles with others. Nearly everyone is susceptible to the disease, but nursing infants, especially under five months of age, enjoy a more or less perfect immunity and although closely associated with measles patients do not always contract it. Indeed, instances have been reported where the infant sucked the breast of a woman with measles without infection. After about one year of age and from that upward, the susceptibility is great and the non-susceptibility of older individuals is to be explained largely by the immunity which they have acquired through having had the disease.

The immunity caused by measles is complete and lasting and second attacks are very rare. The writer has seen one instance of a child having two attacks five years apart. Panum in his large experience did not report a single instance, and Barthez and Sannée report but three. Congenital measles has been reported a number of times, and a pregnant woman who contracts measles may communicate the disease to her unborn child. The child may be born with the rash in the same stage as that of the mother or in the catarrhal stage and the rash may come out later.

Inoculation Experiments.—Hektoen was able to transmit the disease by injecting the blood from the veins of a measles patient into a young man who had never had the disease. On the thirteenth day there was a temperature of 103° and on the following day the eruption appeared. There were no catarrhal symptoms in this patient. In a second case, symptoms began on the eleventh day and the eruption appeared on the fifteenth. Anderson and Goldberger and others have succeeded in transmitting the disease to the Rhesus monkey by taking the blood from a patient just before the eruption appears. They also were able to transmit the disease by using the nasal and buccal secretion, but were unable to do so by means of the desquamating epithelium. Up

to the present time no organism has been described. The virus of the disease is filterable through the finest filters, is easily destroyed by heat, but resists lower temperatures.

Pathology.—The toxemia of measles rarely causes death and the fatal cases are always complicated with other lesions, the most frequent being pneumonia, colitis, and nephritis. The changes in the mucous membranes and the skin are the most striking features. Unna describes the changes in the skin as a spastic condition of the bloodvessels. The ducts of the sweat glands are œdematous and the lymphatics distended, but there is no cellular exudate. There is no mitosis during the inflammatory stage, but karyokinesis may be demonstrated during desquamation. Catrin has described the changes as an infiltration of the skin with a sort of colloid material which eventually leads to coagulation and subsequent desquamation of the dead epidermis. Others describe somewhat similar changes and include cellular infiltration as well. The changes in the mucous membranes are of the nature of a catarrhal inflammation which may affect any part of the body, but the most marked changes are in the conjunctiva, mouth, throat, larynx, trachea, bronchi, and lungs. Focal necroses have been described in the liver.

Incubation.—Symptoms appear from nine to eleven days, and the rash quite uniformly on the thirteenth and fourteenth day after infection.

Prodromal Eruptions.—The prodromal rashes of measles have received but scant attention. Thursfield has called attention to a scarlatiniform and sometimes to a papular rash appearing about twenty-four hours before the regular eruption. J. D. Rolleston has made a careful study of this subject and found prodromal rashes in 30 cases or 42.8 per cent. of all observed. The character of the prodromal rash varies. It is most frequently either a blotchy erythema or scarlatiniform rash. It is usually seen on the trunk, behind the ears, or on the extremities, although occasionally it is noted on the face or neck. The rash is always transient and there is no evidence of irritation.

Symptoms and Course.—After infection there is an incubation period in which there are no very apparent changes, the general health is good and the child does not complain. A loss of weight begins on the fourth or fifth day after infection, according to Meunier, and there is also a leukocytosis during the incubation. Slight changes of temperature have been observed but are not constant and there is no reason to believe that they are of necessity a manifestation of the incubation period. Sometimes there is malaise, depression of spirits, and drowsiness. The tentative diagnosis during the incubation period must rest upon the history of exposure, a loss of weight, and a leukocytosis.

The symptoms may be divided into three stages; the period of invasion or the catarrhal stage, the period of the eruption, and the period of desquamation.

The period of *invasion* is ushered in by numerous symptoms which make the diagnosis probable if there is a history of a previous exposure. About the ninth and tenth day after infection, the child becomes listless and drowsy, and the drowsiness is such a constant feature as to be regarded by some of the laity as almost pathognomonic. The appetite

is poor or lost. If the child is old enough to describe the symptoms there is complaint of headache, a chilly sensation, and of feeling tired. There may be slight or high fever and on this or the following day marked catarrhal symptoms appear. The conjunctivæ become congested and slightly reddened. There is coryza with sneezing, the throat is slightly reddened, and there is some cough and often hoarseness. These symptoms increase in intensity, and after three or four days the child has inflamed and swollen conjunctivæ with usually more or less lacrymation and some photophobia. The coryza is intense and there is severe bronchitis and frequently hoarseness. In some cases these symptoms are mild and there is but little fever, while in the severest cases the child is extremely miserable and may be completely prostrated. The eruption is first visible in the mouth and then appears on the face about the margin of the hair and spreads as described below. The temperature may drop after the rash makes its appearance or continue for a day or two longer. The symptoms are usually most intense about the height of the rash and as it fades they lessen so that by the time the rash has disappeared the child feels completely comfortable. The lymph nodes over the body become enlarged, particularly the post-cervical and post-auricular, but this in some cases may be wanting. They rarely attain the size seen in rubella. The spleen is usually slightly enlarged. Heim has called attention to the odor of measles which is very perceptible in a ward full of measles patients, but is too faint to be detected by the average nose in isolated cases. It is a sweetish heavy odor suggestive of sickness and has been likened to that of freshly plucked goose feathers.

Koplik Spots.—The rash had been noted in the mouth, and excellent descriptions of the spots had been given by Filatow, Flindt, Reubold, and Bohn, but they apparently did not appreciate their clinical significance. Koplik, in 1896, pointed out the fact that the spots which now bear his name are pathognomonic. They appear on the mucous membranes of the mouth, most frequently on the inside of the cheeks about the level of the second molar. They may also be noted on the inside of the lips and sometimes in other places. They appear as a distinct eruption which consists of small irregular spots of a bright red color and in the centre of each spot there is noted, in strong daylight, a minute bluish white speck. Sometimes there are only a few spots, some six or a dozen, while in other cases they may cover the whole of the buccal mucous membrane. They do not coalesce but retain their punctate character. These spots are of particular value in making a diagnosis, as they may be seen twenty-four to forty-eight hours before the eruption is present on the skin and sometimes three or even four days before the exanthem. These spots can be seen in fully 95 per cent. of the cases, if not more, but the examination must be made by bright daylight or by a very white light, as in ordinary artificial light they are not visible. If one is familiar with their appearance there is little or no danger of their being confused with anything else. Thrush or aphthous ulcerations have been mistaken for them, but only by unskilled observers. The opening of Steno's duct should be kept in mind.

Enanthem.—On the first day of the fever there is a slight diffuse redness of the mucous membranes and on the second day there is considerable redness and injection of the pillars of the fauces and of the tonsils; there may be slight swelling of the tonsils. The Koplik spots may be noted at this time or during the subsequent day. On the third day the mucous membrane of the mouth is usually normal in color except for the Koplik spots and the inflammation of the fauces. About this time, or sometimes slightly before, the eruption comes out on the skin and the mucous membranes again become more or less reddened, but more in limited areas and the Koplik spots are lost in an eruption which has the same general characteristics as the eruption on the skin. This is distinct on the fourth and fifth day and usually by the sixth day or a little later there is left only a diffuse redness of the palate and cheeks; sometimes the distinct eruption persists longer. The course of the eruption in the mouth as on the skin varies greatly and no set description will cover all cases. The eruption occurs on all the mucous membranes and is particularly noticeable on the conjunctiva; it has been described on the larynx, the trachea, and bronchi as well as the mucous membranes of the genitalia and bladder.

Exanthem.—"The symptoms increase until the fourth day, when (although sometimes a day later) little spots just like flea bites begin to come out of the forehead and the rest of the face. They increase in size and number, group themselves in clusters and mark the face with large reddish spots of different figures" (Sydenham). The eruption usually appears on the third, fourth, or fifth day after the catarrhal symptoms begin, but it may come out on the first day after the beginning of the symptoms or be delayed as late as the tenth. Variations in the appearance of the rash are more frequent in young children. In rather atypical cases the rash, it is said, may be entirely absent. The rash first appears as small red spots on the temples, the forehead about the edge of the hair, and back of the ears. They are seen a little later or even at the same time scattered over the body, both back and front, and at this time there is often a mottling or marbling of the skin as if the eruption were beginning deep down. The eruption consists of minute pin-head sized papules slightly elevated and as a rule easily felt and these are grouped sooner or later in somewhat crescentic patches about a centimeter in length. The rash spreads from one part of the body to another, the face being first affected, then the body, the arms, and lastly the legs, finally involving the palms of the hands and soles of the feet. In some places the eruption is so thickly set that it forms continuous red patches, which is most usually noted on the face and upper part of the chest. The extent of the eruption varies considerably, and some have but a few blotches, while others may have the entire body almost uniformly covered. The skin is really never affected in its entirety even where the rash is most marked. Normal skin may be made out by pressure or by stretching it. The earlier spots are of a rose red color and rather bright, but later the color is that of a purple raspberry and has a characteristic tint becoming somewhat darker as time goes on until it is nearly a port-wine color or almost the shade of a purple birth-mark.

After several days it fades rather quickly, leaving purplish brown spots which in a day or two become faint yellowish brown. This slight pigmentation persists from two or three weeks and gradually disappears.

The eruption fades in about the order it appeared and may begin to disappear from the face before it is fully developed on the feet and ankles. The small papules are sometimes surmounted by a tiny vesicle, while in others there is merely a small elevated point. Sometimes the papules are large and have a distinct shotty feel. Small petechiæ are common in some cases (about 5 per cent.), particularly about the wrists and ankles. They are easily produced by slightly bruising or pinching a fold of skin between the fingers. This should not be mistaken for a hemorrhagic rash. The true hemorrhagic rash is not very common, occurs in the severest form of the disease, and is spoken of as "black measles." It consists of hemorrhage into or about the great majority of the spots, and coming on early as the eruption appears, it is nearly always the sign of a fatal issue. When it appears later the prognosis is not hopeless, although it is always grave.

There are many curious anomalies, and the eruption may remain incompletely developed and give the appearance of being deep in the skin; it may run an extremely rapid course or be unduly prolonged. It may fade in an irregular manner, remaining longer on the face or elsewhere than would be expected. Sometimes there is considerable itching and the skin may be broken by scratching. Sometimes ecchymotic spots may appear from the same cause. There may be free perspiration in some cases. The rash varies in appearance from many causes. It is made more intense by the patient being in a warm room or a warm bed and it is sometimes the custom to increase the amount of bed clothing to make the room unduly warm in order to "bring out the measles." If the rash is indefinite it may often be brought out by a warm bath, as is sometimes done for diagnostic purposes. Exposure to cold will contract the small arterioles and cause the rash to fade.

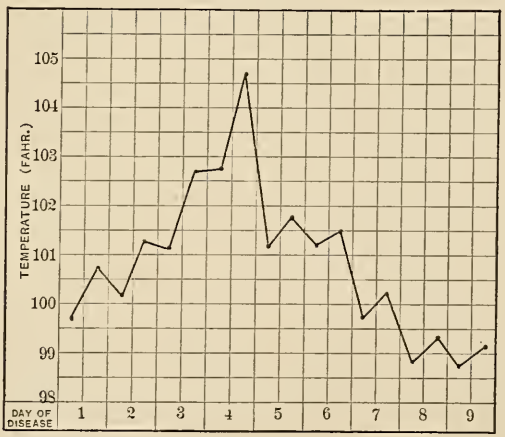
Circulatory failure may also cause the rash to fade. Sometimes a pemphigoid eruption is seen, usually about the fifth or sixth day, but sometimes later and with this is a rise of temperature and marked constitutional symptoms. The vesicles are large and flat often filled with thin pus and sometimes bloody serum. The patches may become gangrenous and death follow or slow recovery may take place. There may be at the same time other complications, such as pericarditis, endocarditis, pleurisy, and arthritis. Sometimes an occasional bulla is seen without the grave prognosis of the pemphigoid form. Gangrene of the skin or of the genitals may follow measles. Furunculosis, impetigo contagiosa, and ecthyma are often mentioned in connection with the rash but belong properly to complications. Occasional late eruptions are seen, and these are usually macular.

Desquamation follows in nearly every case, but may be so slight as to escape detection, and if the skin is cleansed thoroughly and oiled daily the scaling is scarcely noticeable. In ordinary conditions there are small bran-like scales which continue to come away for one or two weeks, or sometimes longer. Measles without an exanthem is an anomaly

which on good authority is said to be occasionally seen. Some of these cases may be explained by measles with a rash of short duration which probably happens more often than the absence of the rash.

Anomalous Cases.—These occur with considerable frequency and the disease may be light with few or no symptoms, little fever, and not much eruption. In other cases the rash may be quite pronounced with but few other symptoms or any of the more noticeable features may be absent. On the other hand, any or all of the symptoms may be very intense either at the onset or at the beginning of the eruption. There may be extreme headache with photophobia suggesting meningitis or convulsions at the onset or intense drowsiness amounting almost to coma. Epistaxis and other hemorrhages may occur especially on the third or fourth day. Catarrhal symptoms of a most intense grade may be present and the bronchitis may be so severe as to cause alarm. There may be croupy attacks or intense hoarseness with symptoms not unlike laryngeal diphtheria. In some rare instances false membranes may form in the larynx due to streptococci or staphylococci, and the obstructive symptoms may be so severe as to require intubation. Neurotic children and those who have had whooping cough may have an intense spasmodic cough difficult to control. Occasionally there are joint pains and even arthritis with effusion.

FIG. 39

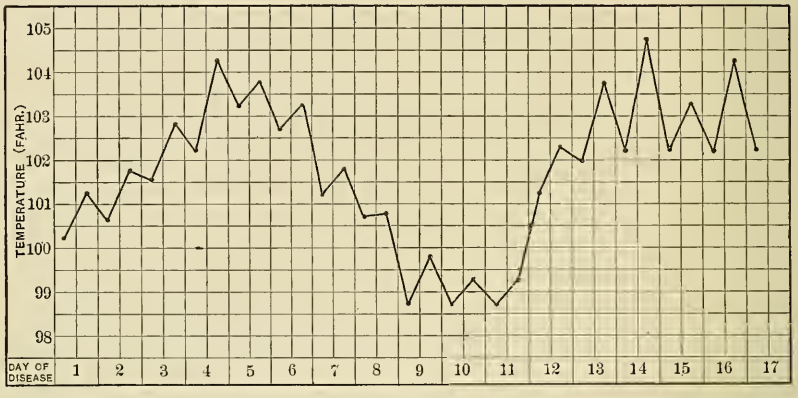


Measles temperature chart, showing sudden fall at the appearance of the eruption. Personal observation.

Malignant Measles.—The disease may at times be of a particular malignant type and this may date from the onset or from the beginning of the eruption. In some instances there is hyperpyrexia, the temperature being continuously high, and death follows with no other symptom of note. Other malignant cases are of the hemorrhagic variety in which usually at the onset of the eruption there are hemorrhages into the skin and from the mucous membranes. There may be high fever with intense prostration, and death may be caused by hemorrhage or the

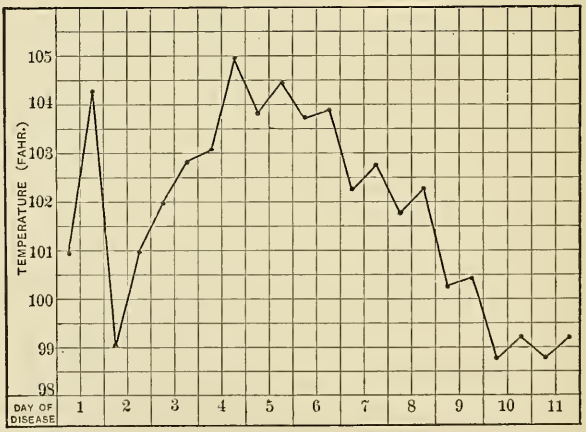
intensity of the toxemia. In other malignant cases there are severe symptoms, such as headache, vomiting, diarrhœa, high fever, a weak, rapid pulse, hemorrhage, and intense nervous features, convulsions or coma, and death.

FIG. 40



Measles temperature chart, showing a complicating pneumonia coming on after the temperature had fallen to normal. Such a temperature can always mean a complication.

FIG. 41



Measles temperature chart, showing initial rise and fall. Personal observation.

Temperature.—As a rule there is no fever during the incubation period, but with the onset of the catarrhal symptoms the temperature begins to rise and reaches 100° or 101° F. in the evening. The following morning it falls as a rule, although it may remain the same or even get higher. The temperature rises every evening to remit slowly on the following morning until the third or fourth day when 104° or 105° F. is reached. With the appearance of the rash, the temperature falls slowly during the next few days and is lower each morning with a slight increase in the evening until normal is reached. This seems to be the most general

course in uncomplicated cases. It not infrequently happens that at the beginning of the symptoms there is a sharp rise to 103° or 104° F. and then after several hours a fall to normal and later the regular rise begins. In exceptional cases the temperature may rise suddenly at the invasion and remain high with slight morning remission until the eruption appears. Another common occurrence is a sudden drop in temperature with the appearance of the rash. In some there is no subsequent rise of any importance. In others the temperature may rise to 102° or 103° F. and then fall during the next two or three days. Any sudden rise in temperature a day or two after the eruption is out may be regarded as an indication of some complication, and if the temperature remains as high as it was for more than a day or two after the eruption has made its appearance, it indicates the same thing. In such cases the respiratory tract, particularly the lungs, should be examined with special care. Otitis media is another and overlooked cause of high temperature.

Blood.—There is a leukocytosis beginning during the period of incubation, reaching its maximum during this period and lasting into the first part of the stage of invasion. During the latter part of the stage of invasion or the beginning of the eruptive stage, the leukocytes fall to normal and there may be leukopenia. During this stage a leukocytosis means some complication, although complications may exist without it. The polynuclear neurophiles are increased during incubation, invasion, and eruption, fall below normal with defervescence, and reach normal in convalescence. The lymphocytes are decreased at first but increased later. The large mononuclears and transitionals are normal at first but are also increased in the later stages, while the eosinophiles are decreased during the eruption but increase later. The myelocytes are present in small numbers during the eruption. The normal leukocyte count is generally reached during the fifth day of the eruption. It should be remembered that the blood findings may be so altered by complications as to be of little value in diagnosis or prognosis.

Urine.—Albuminuria is usually present during the febrile period but nephritis is rare. The diazo reaction is found in about 80 per cent.

Complications.—These are frequent and very important, and it is sometimes difficult to draw the line between symptoms and complications. More or less marked complications occur in over two-thirds of the cases.

Eye.—Injection of the conjunctiva and usually a distinct conjunctivitis with a certain amount of photophobia and often blepharospasm always occur. If the child is kept in a darkened room and some mild antiseptic eye wash applied frequently there is generally no further trouble. Sometimes there is inflammation of the cornea or the inflammation may extend to the lacrymal glands or there may be blepharitis. Sometimes weakness of accommodation may follow measles and occasionally there may be paralysis or spasm of the ocular muscles. Amblyopia is rare and in some cases it has been followed by optic atrophy.

Ear.—Acute catarrh of the middle ear is not infrequent and may cause headache, slight deafness, or tinnitus. Occasionally the inflam-

mation becomes purulent and sometimes there is involvment of the mastoid.

Gastro-intestinal.—Stomatitis is present in every case, usually only catarrhal, but ulcerative stomatitis may be noted and prove serious. Gangrenous stomatitis is occasionally seen; the destruction of tissue is painless and rapid and there is a characteristic fetid odor. Vomiting is not more common than in the other febrile disease of children, and while acute gastritis may occur, disease of the intestine is more frequent, diarrhœa often being present; ileocolitis may be one of the major complications. In the severest form the colon and lower part of the small intestine are affected.

Respiratory Tract.—This is frequently involved and nearly every patient has coryza which may be purulent. The larynx is frequently inflamed with hoarseness, croupy cough, and sometimes loss of voice and symptoms of obstruction. These cases may be difficult to differentiate from laryngeal diphtheria. Severe laryngeal inflammation is always to be regarded as dangerous, and membranous laryngitis is second to pneumonia as a cause of death in measles. Sometimes persistent hoarseness follows the disease.

Tracheitis, tracheobronchitis, and bronchitis are all frequent. The bronchitis may extend into the smaller tubes and bronchopneumonia follow. In the severer forms of this there is marked cough, dyspnœa, and cyanosis, the pulse becomes rapid and weak and death may ensue. The physical signs are the sinking in of the ribs during respiration and numerous fine rales heard all over the chest, while coarse rales are not uncommon. Areas of dulness cannot be made out. The breathing is shallow, the diaphragm in consequence is high, and the liver dulness may be mistaken for consolidated lung.

Bronchopneumonia is the most frequent of the more serious complications and is responsible for more deaths than any other cause. Henoch states that some pneumonia is found in every fatal case. The symptoms, course, and physical signs do not differ from ordinary bronchopneumonia, but it should be borne in mind in measles that the temperature cannot be relied on to differentiate pneumonia and bronchitis. If there are symptoms of bronchopneumonia, even though not marked, it is safe to assume that it is present. Pneumonia may be suspected if the temperature is above the average or if the child is apathetic with rapid and irregular respiration. There is no regular course for this pneumonia as it may last a week with irregular fever or persist for six weeks, the fever running now high, now low, sometimes subnormal, and sometimes above 105° F. The process may stop and go on to recovery at any time. Following bronchopneumonia, especially a persistent attack, there may be bronchiectasis, and chronic interstitial pneumonia is not an infrequent sequel. Bronchopneumonia is frequent in asylums and hospitals and among the poor, and occurs more often in weak than in robust children. It is more common in overcrowded wards than where there is sufficient air space and ventilation. Lobar pneumonia is sometimes seen, and there are cases which may be regarded as abortive pneumonia. The temperature is high for a day or two, the child is prostrated, somewhat

cyanosed, and the respiration rapid, but after one or two days the symptoms and signs disappear. Empyema should always be borne in mind where there have been lung complications, and gangrene of the lungs may follow. In some epidemics pleurisy is frequently noted.

Circulation.—Involvement of the heart is not common unless other complications are present. Pericarditis is sometimes seen, but more frequently escapes notice until the autopsy. Endocarditis and myocarditis are probably due to the complication which caused death.

Nervous System.—Convulsions are occasionally seen at the onset, and headache, backache, and neuralgia are not infrequent. Contractures of the muscles sometimes occur early and during convalescence. Various forms of paralysis, hemiplegia, paraplegia, due to myelitis and general neuritis, have all been reported, but are rare. Temporary insanity, chorea, and epilepsy have all been ascribed to measles.

Skin.—Urticaria, furunculosis, impetigo contagiosa, and ecthyma are the most frequent complications. Erythema nodosum and erysipelas have been reported. Pemphigus is frequent; it may be very extensive and accompanied by severe constitutional symptoms and sometimes gangrene of the skin and death. Gangrene of the skin may occur alone but is usually an extension of gangrene extending about the cheek or vulva. Measles is reported as sometimes having a curative effect upon eczema, particularly upon the facial type.

Bones and Joints.—Arthritis may occasionally be seen, the knee being most frequently affected, and osteomyelitis has also been noted.

Pregnancy and Measles.—Cerf has studied the effect of measles in pregnancy, and his figures show that it causes abortion in 60 per cent. of the cases. The more advanced the pregnancy the more probable is the abortion, and after the seventh month there is premature birth in 80 per cent. There were no postpartum complications in these cases.

Measles and Other Infections.—When measles and chicken-pox are seen together they both run their accustomed course. If the chicken-pox appears first the diagnosis is easy. After the measles rash appears the diagnosis may present great difficulty. Smallpox and measles together may produce a difficult clinical problem. The measles exanthem may be distinguished between the pocks, but if the smallpox is confluent the measles eruption may be indistinguishable on the face. According to Leech, when measles and varioloid are seen together each runs its course uninfluenced by the other. An attack of measles undoubtedly lowers the resistance, and any infection may of course be seen as a complication. Tuberculosis may be regarded as a complication or sequel of measles. Tuberculosis at this time may mean extension from some preëxisting focus, or it may mean an infection from without.

Diagnosis.—This is usually easy after the rash has appeared, although at times it may test the ability of the clinician to decide upon the nature of a morbilliform rash and cases without eruption are almost always doubtful. To be of the greatest preventive value, the diagnosis should be made in the preëruptive stage. The early leukocytosis is of value if a blood-count can be made. If measles is suspected, drowsiness, cough, coryza, and conjunctivitis are sufficient to make a tentative

diagnosis. The Koplik spots are of special value, and the most frequent cause of failure to find them is a lack of knowledge of their appearance, the use of poor or artificial light, and a hurried examination. Meunier has called attention to a loss in weight by the fifth or sixth day of the incubation period.

Scarlet fever is distinguished by the sudden onset with vomiting, high fever, the characteristic rash, the angina, and the strawberry tongue. *Rubella* is easily confused, but in epidemics the absence of catarrhal and other symptoms, the absence of Koplik spots, and the presence of the characteristic enanthem and especially the polymorphous character of the exanthem make the diagnosis easy. *Smallpox* is the most important disease with which measles may be confused. Despite the apparent difference, the two diseases may be strikingly similar, especially about the beginning of the rash. Measles is perhaps more often mistaken for smallpox than the reverse. In smallpox there is usually an initial chill, vomiting, backache, and fever, and when the eruption appears the fever falls and the patient feels comparatively well. It should be remembered that in some cases of measles there may be severe symptoms at the onset and with the appearance of the eruption the temperature may fall, although this is not the rule. If the measles rash happens to have a distinctly shotty feel the clinical picture may be almost, although not exactly, the counterpart of smallpox. The measles enanthem is finer, much more abundant and more in patches than the eruption of smallpox as seen in the mouth. On the first day or two of smallpox there are small red papules seen best on the palate. If Koplik spots are present they are of great aid, but they may be obliterated before the patient is seen. The exanthem of measles is frequently on the face, chest, and back, while smallpox is not confluent as a rule on the trunk, but frequently so on the face, forearms, and wrists. The measles eruption is arranged in crescentic patches while the smallpox eruption is not. The history of exposure to one disease or other is of some value, but if doubt exists it is better to isolate the patient and wait for twenty-four hours, when the diagnosis is usually clear. The prodromal rashes in smallpox may be morbilliform and have been mistaken for measles, but the absence of Koplik spots and catarrhal symptoms render it plain that the rash is not measles whatever else it may be. *Typhus fever* has the same catarrhal symptoms but as a rule the general symptoms are more intense. The onset is more sudden and the eruption becomes hemorrhagic after the first, second, or third days and consists rather of spots and blotches. *Influenza* may be mistaken for measles at the onset and also a septic infection with an eruption. The absence of catarrhal symptoms and of Koplik spots is of considerable value. *Syphilitic rashes* may occasionally be morbilliform, and if there is fever at the same time may be mistaken for measles. The presence of other manifestations and the longer duration of the rash are the most distinguishing features. The enanthem in these cases is of particular diagnostic value. *Serum rashes* are usually scarlatiniform or urticarial but may occasionally resemble measles. They may be distinguished by the absence of the characteristic enanthem and prodromes. *Drug rashes* are extremely

liable to be confused with measles as there are a number of drugs which may cause a morbilliform rash. The history of taking the drug, the absence of symptoms and of fever usually render the diagnosis plain. Antipyrine is the most frequently used drug which produces a measles-like eruption. The arrangement is less crescentic than in measles, and unlike measles, it does not tend to spread after it once appears. Quinine rashes at times may resemble measles and may even spread from above downward. Copaiba, cubebs and other balsams, ethereal oils, turpentine, chloral, and others, may cause a measles-like eruption. In one instance the writer saw the rose spots in typhoid fever so numerous as to suggest measles but there was no crescentic arrangement and no other symptoms suggestive of measles.

Prognosis.—This must be guarded in any given case. Measles is usually regarded by the laity as a mild disease but a very large number of deaths are caused by it. The mortality varies in different epidemics between 3 and 50 or more per cent. It varies greatly with the age and surroundings. In private practice among the better class measles is not a dangerous disease, but among the poorer classes and in hospitals and asylums it may prove a veritable scourge. Age is an important factor, and from birth to six months of age there are few deaths owing to the comparatively few cases. From six months to two years of age there is a steadily increasing death rate which then declines until about the fifth year, after which deaths from measles are comparatively infrequent. The sexes are affected about equally. After forty the mortality increases with the age so that in old age it is an extremely fatal malady. There are more deaths in cold winter weather than in summer, partly owing to the greater number of infections but largely due to the greater number of pneumonia cases. Death is nearly always due to complications the most frequent fatal ones being bronchopneumonia, bronchitis, laryngeal affections, diarrhœa, ileocolitis, tuberculosis, and noma.

Prophylaxis.—Nearly everyone has had measles at some time, and many of the laity take no pains to guard their children from infection. As the mortality decreases after two years of age and is comparatively slight after five years, every effort should be made to put off infection until after the fifth year. Quarantine is without doubt the best means for preventing the spread of measles. Susceptible children and indeed all visitors should be prevented from entering houses where there are cases of measles and when this cannot be done the patient should be removed if possible to the Municipal Hospital. School inspections have done much to lessen measles and children under suspicion should not be allowed to attend. Any child with suffused eyes, cough, and sore throat should be sent home to await developments. During severe epidemics, public and private schools should be closed and children's parties should be prohibited.

Isolation.—In hospitals and institutions for children every suspicious patient should be isolated. Large hospitals for children would do well to have a quarantine ward in which children who have not had measles can be isolated from the remainder of the inmates until two weeks have

passed, as in nearly every instance epidemics in hospitals are started by the admission of a child in the incubation period. The isolation room or ward should be in a detached building allowing a free air space all around it. Where this is not practicable the room should be as far removed as possible and be strictly quarantined from the remainder of the building. Isolation in small hospitals and in private houses unless carried out in this manner is liable to prove futile. Isolation in a small room off the end of a ward may do better than no isolation at all, but certainly where children are concerned it is not very useful. The difficulty in isolation consists of the fact that it can rarely be done sufficiently early. The disease may be transmitted before its presence is ordinarily suspected, and the children with whom the patient has come in contact are infected before the disease has been diagnosed. This is particularly true in private families where the question of isolation is an open one, but if the susceptible children can be sent away as soon as the disease is discovered that is the best thing to do. Such children should not be sent to homes where there are other susceptible children as the children so sent are frequently infected and may prove a danger to others. If isolation is enforced in the average household it is usually not strict enough to be of service or is started too late. The question of disinfecting the rooms occupied by the patient is important. In hospitals and in institutions it should be done and also in private houses where the rooms are to be occupied immediately by susceptible children, but if two or three weeks elapse there is no danger, even if there is no disinfection. After measles it is well to give the apartments a thorough cleaning and have them well aired for several days.

Treatment.—The child should be placed in a convenient room, and plenty of fresh air is desirable; but ventilation should be accomplished without strong drafts, which may often be done by ventilating through an adjoining room. The temperature should be about 70° F., and kept as equable as possible. There is no advantage in superheated rooms, an idea very prevalent among the laity. As there is usually photophobia the room should be sufficiently darkened to be comfortable.

It is well to have the skin anointed with some bland ointment, and equal parts of vaseline and lanoline will be found satisfactory. The skin is kept clean by sponging with warm water and castile soap twice daily, after which the ointment is applied. If there be itching, sponging with warm carbolic acid solution (1 per cent.) is useful. There is a rooted objection in most families to using water on measles patients, and when this cannot be overcome or when the child is liable to be chilled by exposure, all attempts at sponging are best abandoned.

The diet should be the same as for any acute fever. Bottle-fed infants should have their food diluted, and older children should be placed upon liquid diet. Food should be given at regular intervals, two, three or four hours apart, depending on the amount given at any one time. Plain or carbonated water, lemonade, orangeade, grape juice, and water, and similar drinks may be used to allay thirst, and if food is not well taken egg albumin may be given. Alcohol may be used if indicated. After the subsidence of the fever a gradual return to solid food should

be made. If gastro-intestinal disorders appear, the usual rules of diet for these should be observed.

Fever.—If this is but moderate, one of the old-fashioned fever mixtures, such as spiritus ætheris nitrosi (♏ij to ♏xx) and liquor ammoni acetatis (♏v to ℥j), in an aromatic syrup, may be used. Citrate of potassium (gr. j to v) is also frequently given in syrup of lemon. If the temperature is high and the child restless a tepid or sponge bath is the best means of controlling it. If there is any objection on the part of the family to the use of water, this may be overcome by advising sponges of half alcohol and water or even more dilute solutions. A cool pack or a cool bath may be used where the other means do not bring the temperature down. A temperature which does not go above 104° or 104.5° F. need not be reduced unless attended by other symptoms. Temperature over 104.5° should always be reduced. An ice-bag to the head is grateful if there is headache. In giving cold baths to measles patients care should be taken to avoid exposure. If the feet become blue and cold, warmth and friction may be applied to them, and an alcoholic stimulant administered. If the temperature is high and the child feels cold to the touch a warm bath is indicated. Antipyrine is useful in patients with a good strong heart, but need not be given for the fever alone. It is useful in combating nervousness and cough.

Nervousness and Sleeplessness.—These are frequently allayed by bathing or sponging. If these do not suffice, codeia and antipyrine may be given. A child of one year may be given $\frac{1}{24}$ of a grain of codeia with one grain of antipyrine in syrup of orange. This may be repeated, and will be found most useful for controlling nervous irritability and cough. Phenacetine may be given for the same purpose.

The Eyes.—The conjunctivitis present in all cases requires the usual treatment of a mild antiseptic eye wash. Ten grains of boric acid with 1 dram of camphor water and 7 drams of distilled water is suitable. If the lids are found adherent in the morning, the edges should be anointed at night and once or twice daily with a salve containing 1 grain of the yellow oxide of mercury to 4 drams of vaseline.

The Nose, Throat, and Mouth.—These should be kept clean by douches, sprays, or gargles. As a rule the nose is best kept clean with a nasal douche which flushes without any pressure, thus avoiding the possibility of forcing the secretions up the Eustachian tube. Dobell's solution is satisfactory for this purpose. The throat is usually best cleansed by using Dobell's solution in an atomizer, but older children may use a gargle. The mouth should be kept clean by a spray or by absorbent cotton wrapped about the finger, and moistened with boric acid solution, Dobell's solution, or diluted peroxide of hydrogen.

Laryngeal complications are best treated by inhalations, of which creosote, oil of eucalyptus, or compound tincture of benzoin are the most efficient. A dram (4 gm.) to a pint (500 cc.) of water may be used. This is also useful in bronchitis and bronchopneumonia. External applications—heat, cold, or counterirritants—may be made over the larynx.

Bronchitis.—Inhalations as advised for laryngeal complications will be found useful. Antipyrine and codeine will be found of service. Heroin

and hydrochloride may be used if the cough is very irritable. Brown mixture with or without ammonium chloride may be used in older children, and syrup of squill is also useful. The Jackson mixture, consisting of equal parts of syrup of squil, syrup of tolu, oil of sweet almond, and mucilage of acacia, given in doses of from one-half to a teaspoonful, if often helpful. Drugs which nauseate are best avoided.

Bronchopneumonia.—This is treated as under ordinary circumstances; inhalations, counterirritation, and stimulants, as indicated, are the best forms of medication. The chest should neither be weighed down with plasters nor poultices, nor should heavy jackets and innumerable undershirts be used. The chest should be allowed full freedom and the air of the room should be kept fresh, and gas stoves and unnecessary attendants excluded.

Gastro-intestinal Complications.—Vomiting is one of the most troublesome complications, and is best treated by withholding all food and giving the stomach a rest. If this does not avail and if the patient is under a year of age or sufficiently tractable the stomach may be washed out. A useful prescription is equal parts of cinnamon water and lime-water, of which a teaspoonful may be given fifteen minutes before feeding, and repeated several times if necessary. Effervescing drafts are also useful. Diarrhœa and ileocolitis are best managed by cleaning the intestinal tract and careful dieting. Bismuth subnitrate is most useful.

RUBELLA

Definition.—Rubella is a specific infectious disease occurring in epidemics, characterized by a polymorphous rash which sometimes resembles that of measles, sometimes that of scarlet fever, and sometimes that of both diseases; by little or no constitutional disturbance, and by almost constant enlargement of the cervical and sometimes other lymph nodes.

Etiology.—Rubella exists as a separate disease, and an attack does not protect against either scarlet fever or measles, nor does an attack of either scarlet fever or measles protect against rubella. It occurs in epidemics and is rarely seen sporadically. The sporadic cases are usually part of small family or school epidemics.

Rubella may be transmitted by direct contact and by fomites, especially clothing or bedding, but the contagious principle has not yet been discovered. The contagiousness seems to vary in different epidemics. Steiner does not believe it at all contagious. Atkinson and most observers regard it as contagious only to a slight degree, while Edwards, Griffith, and others, regard it as very contagious. In a small epidemic oberved by the writer there were 14 cases in a ward containing 22, or 63.6 per cent. The disease was not carried to any other part of the building, although the maids and nurses went about freely and the clothes were sent to the laundry without sterilization. The children with rubella were up and went through the same halls as the other children, but used a separate play-room and were not allowed to come in contact with the children belonging to other dormitories. In this epidemic it appeared

as a disease transmitted by direct contact and not by fomites or a third person. The disease is contagious early, perhaps even before the eruption appears, and this lasts as long as the eruption. Comby states that the contagiousness disappears with the eruption.

Sex and Age.—The sexes are affected equally. Scholl has reported a case where the pregnant mother (seven months) transmitted the disease to the unborn child, the disease making its appearance several days after birth. Young infants are as a rule immune. It is most frequently seen in early childhood, while other children and adults are less frequently affected. Hatfield states that the liability varies inversely with the age, whilst Ashby regards adults as even more liable if exposed.

Station in Life.—The disease is more frequent among the poor than the well-to-do, which may be explained by the lessened resistance and the greater danger of exposure.

Immunity.—One attack generally protects and second attacks are very rare.

Incubation Period.—This is ordinarily stated as being from fourteen to twenty-one days. The shortest period is one day (Griffith and Atkinson) and the longest four weeks (Klaatsch).

Symptoms.—Prodromes.—There may be none at all, the rash being the first thing noted; or there may be some indisposition from several hours to two days, and exceptionally as long as four days, before the rash appears. The most common prodromes are headache, backache, loss of appetite, nausea, and sometimes vomiting, slight fever, drowsiness, and, in some, agitation. Convulsions have been reported at the onset and occasional symptoms are redness of the eys, a little dysphagia, some hoarseness, and occasionally sneezing.

Invasion.—This may be slight or severe. In some the only thing noted is the appearance of the rash, or there may be chilliness, languor, headache, with pain in the back and extremities. There may be more rarely coryza, congestion of the conjunctivæ, slight pharyngitis, hoarseness, cough, nausea, and vomiting. There may be epistaxis, and Priolean has reported an initial hemorrhage from the eyes and ears. Urticaria and other rashes may precede the initial eruption. The stage of invasion may last from several hours to five days; these symptoms show great variations and may disappear before the eruption.

Temperature.—This varies greatly in different epidemics. There may be no fever at all or it may in rare instances reach as high as 104.3° F. When the temperature is high it remains so but a short time. In the average case the fever is slight and lasts from two to four days, ranging from 100° to 102.5° F., with slight evening exacerbations. The highest temperature is seen usually at the beginning of the eruption, and to a certain degree corresponds to it, the most marked rashes being attended with the highest fever. The exacerbations which follow never reach as high a point unless there is a relapse or some complication.

Eruption.—The most characteristic feature is the polymorphism, and in one patient it may resemble scarlet fever rather closely; in the next it may be like measles, while in a third it may on one part of the body resemble scarlet fever and on another measles. It may be accompanied

by itching or burning, while at other times there are no abnormal sensations. In the majority it affects the face and scalp first, then the neck and body, spreading from above downward, involving the arms, and lastly the legs and feet. It may spread irregularly and on certain parts of the body be more intense than on others. When more or less continuous pressure is made on the skin, as about the waist or neck band, or on the back or side when the child is in bed, the eruption is more marked. There are patches about the lips in most instances. The eruption may be seen on the palms and soles. In the writer's experience the morbilliform rash is more frequent, and it may be that alone or mixed with other varieties. It is not uncommon to have a measles-like rash over the face and most of the body, while over the parts pressed upon, the buttocks and the inner sides of the thighs, it is a scarlatiniform rash. The rash frequently can be seen in the deeper layers. bluish red macules rather crescentic in shape mottling the skin like marble. Later these appear as rose-red spots, made up of numerous small pin-head-sized papules, slightly raised above the surface, and to the touch like shot under the skin. In some the patches are discrete and in others they may run together. The early rash may at a glance suggest flea or other insect bites. In still other cases the little pin-head-sized papules may be nearly all discrete. The rash fades rather quickly and may be fading on one part of the body while spreading on another. The eruption reaches the greatest intensity usually on the second day and then begins to fade, the entire process lasting from one to two days to a week. The duration of the rash is extremely variable, and it may last but an hour or two or as long as fifteen days. The average duration has been stated as from one to six days, three to four days, and four to five days. The variation in the length of time the eruption lasts is one of the distinctive features. Cases without any eruption have been reported.

Following the fading of the rash there may be a light brownish-yellow discoloration of the skin, which disappears completely in from one to three weeks. There may be the separation of fine bran-like scales for several days or no apparent desquamation. Purpuric spots, vesicles and petechiæ over the entire body have been mentioned.

The Eruption in the Mouth.—Forcheimer has called attention to the eruption which is seen in the mouth, and this in the writer's experience is a constant feature, being noted at the time of the appearance of the rash on the body. Forcheimer describes it as follows: "It consisted of a macular, distinctly rose-red eruption, upon the velum of the palate and the uvula, extending to, but not on, the hard palate. The spots were arranged irregularly, not crescentically, of the size of large pin-heads, very little elevated above the level of the mucous membrane, and did not seem to produce any reaction upon it." This eruption lasts for twenty-four hours or less, but in some cases it can be seen on two successive days. This eruption in the mouth is unlike that seen in measles and also differs from the scarlet fever angina.

The Blood.—There is a leukocytosis (polynuclear) during incubation, followed by leukopenia when the eruption appears. After the disappearance of the eruption the blood becomes normal.

Lymph Node Enlargement.—This is a marked feature; there is a striking enlargement of the posterior cervical lymph nodes present in nearly all cases. It may also affect the submaxillary, postauricular, and suboccipital nodes. The size varies; they may be small or as large as a pigeon's egg. The enlargement comes on about the same time as the rash, but may precede it several days. The swelling gradually subsides with or after the disappearance of the rash. The nodes do not suppurate.

Malignant Rubella.—Edwards and others have reported fatal cases with vomiting, convulsions, delirium, and high fever. The temperature was high (104° F.) and the heart weak and rapid. The pulse rate in some cases was 150 or over and in some there was heart failure. Pneumonia and diarrhœa were the most common complications.

Complications.—These are rare, but occasionally one or more of the following may be observed: pneumonia, pleurisy, bronchitis, croup, earache or otitis, arthritis, erysipelas, stomatitis, temporary enlargement of the thyroid, convulsions, or delirium. Complications are so rare that they may almost be regarded as coincidences.

Relapses and Recurrences.—Recurrences are very rare as the immunity is apparently perfect and lasting. Relapses are rare but do occur and were a marked feature of the Malta epidemic.

Diagnosis.—The polymorphous rash, the eruption on the uvula and soft palate, and the glandular enlargement with an absence of other symptoms, are the most important features. Rubella occurs in epidemics, and sporadic cases are to be looked on rather as measles or scarlet fever. It must be distinguished from drug rashes, especially that from copaiba. The so-called roseola simplex due to heat or indigestion and so common in infancy must not be confounded with it. Dukes has called attention to a rash caused by handling certain varieties of caterpillars, which might be mistaken for rubella. Comby gives the absence of the diazo reaction as one of the signs in differentiating scarlet fever, and the absence of Koplik spots and catarrhal symptoms is of especial value in excluding measles.

Prognosis.—This is almost invariably good. Fatalities are so exceptional as to be regarded as due to the accidental association of some other disease. Epidemics have been reported with a considerable mortality, as one by Edwards in which it was 4.5 per cent.

Treatment.—This is very simple. If the child has fever he should be kept in bed; but if there is no fever and the child feels well there is no danger in allowing him to be about. Small doses of spirits of nitrous ether may be given if there is fever, and phenacetine, with small doses of codeia, if there is much restlessness and nervousness. As a rule no treatment whatever is required.

THE FOURTH DISEASE

In July, 1900, Dr. Clement Dukes, physician to the Rugby School, published a paper in the *Lancet* describing an infectious disease which he called "The Fourth Disease." This affection has been discussed

at considerable length by numerous observers. The incubation period was about the same as that of German measles, nine to twenty-one days. Prodromes were usually absent, but malaise and some sore throat were sometimes present at the onset of the rash. The rash appeared rapidly and covered the body in a few hours. Dukes does not mention whether it appeared on the face or not. The color of the rash was said to have been brighter than that of scarlet fever and was followed sometimes by slight and sometimes by marked desquamation. There was some glandular enlargement. The temperature was usually not over 101°, but in one instance it was 104° F. There were no sequelæ and the attack did not protect the individual against either scarlet fever or rubella. For further information the reader is referred to Dukes' original article and to a discussion of the subject by Ker.[1] The latter renders what he calls the Scottish verdict of "not proven," which is generally accepted.

ERYTHEMA INFECTIOSUM

Definition.—Erythema infectiosum is a feebly contagious disease of childhood characterized by a maculopapular, rose-red rash, especially marked on the face and the external surfaces of the extremities, and by slight or no subjective symptoms.

Etiology.—The exciting cause is unknown, and no organism has been described. The disease usually occurs in epidemics, most frequently in spring and summer, and children between the ages of four anf twelve years are most often affected. It is but feebly contagious, and close contact is required to communicate the disease. An attack does not protect from measles, scarlet fever, or German measles.

Pathology.—No autopsies have been reported, and the only lesions known are erythema and occasionally slight pharyngitis.

Symptoms.—The incubation period has been from six to fourteen days in the cases in which accurate observations could be made. There may be slight prodromes, as malaise and sore throat, but usually the appearance of the eruption is the first sign of the disease. On the first day the rash appears on the face and is described as a rose-red efflorescence which covers the cheeks, extending to the nasolabial folds in front, to the temples above, and laterally as far as the angles of the jaw. Over this area the rash in confluent, slightly raised above the surface. and for the most part sharply outlined, although in places it may fade gradually into the healthy skin. The general appearance is that of erysipelas, but while the skin is hot to the touch it is not sensitive and does not itch. There is no subcutaneous hemorrhage on pinching the skin. The rash disappears on pressure but reappears quickly when the pressure is removed. On the following day the eruption extends to other parts of the body, and on the forehead and chin there are discrete patches. It spreads slowly downward, and on the trunk there are discrete somewhat crescentic patches, from an eighth to half an inch long and suggesting measles, which may also at times be wheal-like, resembling urticaria.

[1] Ker, *The Practitioner*, February, 1902, lxviii, 139.

DIFFERENTIAL DIAGNOSIS OF RUBELLA, SCARLET FEVER, MEASLES AND ERYTHEMA INFECTIOSUM.

	RUBELLA.	MEASLES.	SCARLET FEVER.	ERYTHEMA INFECTIOSUM.
CONTAGION	Apparently varies in epidemics. Direct contact. Possibly from fomites, not through the air.	Highly contagious. By direct contact. By fomites. Through the air.	Marked. By direct contact. By fomites.	Feeble. Usually by direct contact.
INCUBATION.	Variable average 1 to 3 weeks.	Average 9 to 14 days.	Average 1 to 6 days.	Average 6 to 14 days.
PRODROMES.	Slight and of short duration. Occasionally a day or two of malaise.	3 to 4 days. Drowsiness and catarrhal symptoms.	Short or wanting —onset usually sudden.	Very slight and of short duration.
KOPLIK SPOTS.	None.	Present in 90 or 95 % of cases.	None.	None.
VOMITING.	Rare.	Occasional.	Common.	Uncommon.
FEVER.	Slight—average 1 to 2 days, sometimes for 4 days, seldom more than 101 to 102 degrees.	Marked high curve lasting about a week, average from 102 to 104 degrees.	High fever lasting about a week, averages 104 to 105 degrees.	Little or none.
CATARRHAL SYMPTOMS.	Slight.	Marked.	Absent.	None.
TONGUE.	Slight coat, nothing characteristic.	Tongue coated, that of any fever.	Strawberry, later mulberry tongue.	Sometimes slightly coated.
THROAT.	Small punctiform red spots over uvula and palate. Pharynx slightly reddened.	Moderate pharyngitis and redness of mucous membranes.	Usually a severe angina.	Sometimes very slight sorethroat at onset
DIARRHŒA.		Frequent.		
LYMPH NODES.	General enlargement, especially of post cervical nodes.	Postcervical, postauricular, and submaxillary nodes enlarged.	Depends on extent of throat involvement, glands at angle of the jaw involved.	Not enlarged.
PULSE.	Varies with fever.	Varies with fever.	Very rapid.	Normal.
ALBUMINURIA.	Rare and slight.	Rare.	Common.	None.
ERUPTION.	Begins on face, spreads to neck and breast then to arms, legs and feet. Is fading from older parts while spreading to new. Two forms—common form, morbilliform, small, slightly elevated papules, discrete, sometimes confluent, more rarely scarlatiniform, lasts 2 to 4 days or less, color rose-red but this varies.	Begins on face, spreads gradually over entire body. Covering it by the second or third day, consists of small papules arranged in crescentic groups, these are confluent in places, lasts 4 to 5 days. Is deep red, often purplish.	Begins on neck and chest spreads slowly over entire body —maximum about the fourth day. Does not affect lips. Consists of small punctate spots or a diffuse blush, disappears on pressure, lasts about a week. Intense red color.	First on face as symmetrical, rose-red blush, for the most part sharply defined and resembles erysipelas. It is hot to the touch but not sensitive and it does not itch. The second day it spreads to the body and extremities, small discrete crescentic patches over the body and sparingly on the inner and flexor surfaces of limbs. Marked map-like eruption on outer and extensor surfaces. Begins to fade on face in 4 or 5 days. Lasts altogether 6 to 10 days.
DESQUAMATION.	Slight and branny.	Branny.	Marked in flakes and large pieces.	None.
CONVALESCENCE.	Rapid, no complications.	Slow, frequent complications as pneumonia. Later other infectious diseases as tuberculosis.	Slow, complications frequent as nephritis, otitis media, etc.	Rapid, no complications.

The eruption is marked on the extensor and outer surfaces of the arms and legs, and about the elbows and buttocks it may be confluent. Over the extremities the rash is morbilliform and the spots run together, forming map-like areas, which are especially marked when the eruption begins to fade. Shaw suggests that it resembles lace work. The color varies from a rose red to a brownish red. The hands and feet are the last places to be affected, and the mucous membranes are not involved. The eruption fades first from the face after four or five days, and a few days later disappears from the body. In all it lasts from six to ten days, and in some cases may disappear and then reappear after a short time. There is no subsequent pigmentation or desquamation.

There are practically no subjective symptoms, although there may be a slight sore throat at the onset and the tongue may be somewhat coated. There is no glandular enlargement.

Diagnosis.—This depends largely upon the recognition of the rash, and is not difficult. The following are the most striking points of difference: *Scarlet fever*—Marked constitutional symptoms, high fever, strawberry tongue, angina, and a uniform rash. *Measles*—Marked consitutional symptoms, fever, catarrhal symptoms, and Koplik spots. *Rubella*—Enlarged lymph nodes, especially the posterior cervical, and the presence of the eruption over the soft palate and the uvula. *Drug Rashes*—The history of taking drugs. *Urticaria*—The itching. *Erythema exudativum multiforme*—This begins on the hands and feet, becomes vesicular, lasts for weeks, and is attended by marked constitutional symptoms. Erythema infectiosum is not to be confused with the so-called "fourth disease," in which there is said to be a scarlatiniform rash making its appearance in a few hours and often followed by desquamation.

Prognosis.—This is favorable, as there have been no fatal cases reported, and there are neither complications nor sequelæ.

Treatment.—There are no indications for treatment.

MUMPS

Definition.—Mumps is a specific infectious disease characterized by fever and by swelling and tenderness of the salivary glands, usually of the parotids, but sometimes of the submaxillary and sublingual glands. Metastases occasionally occur in other organs.

Etiology.—Mumps occurs in epidemics, especially in schools, colleges, and barracks, and is endemic in the larger cities. Epidemics are apparently uninfluenced by weather or climate, and the sexes are about equally affected.

The majority of the cases occur in children between five and fifteen years of age. Under five years the susceptibility to the disease is not great, and after fifteen it apparently diminishes with age. Nursing infants are usually immune and may not contract the disease even when nursing the breast of a woman with mumps; but cases have been reported during the nursing period. The disease may be transmitted through the placental circulation. White relates a case of a woman whose child showed signs of the disease six days after delivery, and the woman

herself had swelling of the parotid on the following day. Individuals of sixty or seventy years are not immune, and cases may occasionally be seen at that age.

Epidemics in institutions are usually slow and last several months, new cases developing from time to time; from one-quarter to one-third of those exposed take the disease. They are often confined to one set of buildings or to one enclosure.

The disease is transmissible evidently before the symptoms appear, and for some time, even as long as six weeks, after they have disappeared. Transmission is usually by direct contact, and the disease is not transmitted through the air and only rarely by a third person or by fomites. Roth relates a case contracted by sleeping in a bed previously occupied by a patient with mumps, and instances are on record of a nurse infecting other persons.

Incubation Period.—This is usually long and is variously stated by observers. Roth placed the average at eighteen days, with a minimum of four days and a maximum of twenty-five days, while the commission appointed by the Clinical Society of London set the incubation from fourteen to twenty-five days. However, the average period is nearer three weeks than two. There are undoubted cases in which the disease has developed after thirty-five days, and even after six weeks.

Immunity.—One attack generally confers immunity; but second attacks are by no means rare, and even third attacks have been reported.

Bacteriology.—A number of organisms have been described. The most interesting and complete report is by Laveran and Catrin. They obtained an organism in pure culture by puncturing the parotid gland, from the testicle, the œdematous tissue, and the blood. The organism was a micrococcus occurring in pairs (diplococcus), which grew on ordinary media and was easily stained but was decolorized by Gram's method of staining.

Pathology.—But few opportunities have been afforded for pathological study. There is an intense hyperemia and œdema of the gland, with considerable infiltration around it. There are no subsequent changes in the gland.

Symptoms.—Prodromes may or may not be present. They are usually noted in about one-third of the cases, and come on from twelve hours to two days before the swelling appears; but in some cases there may be prodromes from four to even eight days. The usual prodromes are fever with or without a chill, general malaise, vertigo, drowsiness, vomiting or diarrhœa, and epistaxis, and there may also be sweats, fainting spells, pain in the ear, and trismus. The symptoms proper are principally the glandular swelling, pain, and fever. The parotids are usually affected, and one or both sides may be involved. The gland enlarges rather rapidly for from three to six days, then remains stationary for a day or two, and gradually subsides. The subsidence is usually complete in a week or ten days, although in severe cases it may be three weeks or a month before the enlargement has disappeared entirely. The left side is more frequently affected than the right, and where both sides are not affected at the onset the opposite side is generally involved

in from one to four days. In some instances it may be a week or more before the other side enlarges, or only one gland is affected. All grades of intensity may be seen, and there may be light cases which could be very properly termed abortive. In these there is slight fever with a little tenderness and swelling which disappears in three or four days. The average case presents a large rounded swelling at the angle of the jaw, with the lower edge of the lobe of the ear as its centre. The swelling is somewhat boggy at first but does not pit on pressure. Later it becomes very tense, rather firm, and the skin over it is stretched and glazed. In some cases there is a little redness, most marked just back of the ear, while in others there is a considerable blush of the skin and exceptionally an almost erysipelatous redness.

In the most severe forms, which are rather rare, there may be enormous swelling and œdema of the tissues which may extend all around the neck and head and as far as the outer end of the clavicle. These patients present a grotesque, unrecognizable appearance.

The submaxillary glands may be affected after the parotids. In some cases the submaxillary glands alone, or the submaxillary and the sublingual glands, may be attacked without any involvement of the parotids. The sublingual glands are less commonly affected, although they may be attacked after the parotids or by themselves without any further lesion. The sublingual tissues may be involved without any distinct glandular involvement.

Pain is almost a constant symptom, although exceptionally absent. It is located in the swollen gland, back of the jaw, in the temporomaxillary articulation, and often down the neck. The pain is increased on pressure, on mastication and salivation, and is rendered acute by taking acids, as lemon juice or vinegar, into the mouth; and even the sight of them may cause pain in neurotic subjects.

The throat cannot be said to be involved except in severe cases, when there may be swelling due to the œdema. The tonsils may be pushed inward by this and if large may render swallowing very difficult. Some have described an enanthem, but this may be regarded as a complicating stomatitis.

Fever is nearly always present. It may precede the swelling or come on about the same time, and usually ranges from 102° to 103° F., but may be much higher. It disappears as the swelling subsides or sometimes several days before. After an attack of mumps there may be a subnormal temperature for some days. The jaw is usually stiff and in some cases the trismus may even precede the swelling. The saliva may collect in the mouth owing to a slight increase in the secretion and the difficult or painful swallowing, while in other cases there is a decrease in the saliva and consequently a dry mouth. In unusual cases there may be little or no pain, fever, or constitutional disturbance, and the swelling in such cases is usually slight.

Complications.—These are numerous and vary greatly in different epidemics. In one epidemic one particular complication may be quite frequent, as epistaxis, while in other epidemics another complaint, as abdominal pain or diarrhœa, may be common.

Metastasis.—Other structures of the body may be involved, most frequently the testicle in the male, and in the female, the breasts, ovaries, and labia majora. Swelling of the inguinal glands occurs in both sexes.

Orchitis.—Exceptionally this may occur early, before the parotids are affected; and instances have been recorded where in epidemics it was the only lesion. As a rule, orchitis begins at the time when the parotid swelling is subsiding; but it may come on after the parotid swelling has disappeared entirely. There is a return of the fever and constitutional symptoms, and these latter are often severe, although occasionally absent. The testicle swells, becomes tender and painful, and the swelling continues for three to five days or longer and then subsides. Following such an attack there may be atrophy of the testicle. Orchitis is uncommon in infancy and not often seen until puberty or later. Ovaritis occurs in the same way. There is pain in the pelvic region, with swelling and tenderness of the ovary, and this lasts about the same length of time as orchitis. The breasts may become swollen, hard, and painful, and males as well as females may be affected. The prostate may be involved and cases of urethritis have also been reported. Other glands may occasionally be affected, as the thyroid, which becomes swollen and tender. There may be swelling of the lacrymal glands.

Pancreatitis.—The symptoms come on between the first and the twelfth day, usually between the third and the sixth, and last from two to seven days. There is pain between the xiphoid cartilage and the umbilicus, sometimes radiating along the costal arches and to the back. There is pain in the epigastric region on pressure and at times nausea, vomiting, and diarrhœa. Tenderness over the pancreatic region is not an uncommon occurrence in the course of mumps.

Eye.—These are chiefly of an inflammatory nature, with the usual symptoms. External œdema about the eyes with marked chemosis may render the patient well-nigh unrecognizable.

Ear.—The most frequent is deafness, and in about half the cases it is bilateral. There may be tinnitus and sometimes other symptoms. If the deafness is due to a central disease the prognosis is bad. Usually the deafness comes on about the fourth or fifth day, but sometimes as late as the tenth or even the fifteenth day.

Nervous System.—Symptoms resembling meningitis may come on and may follow orchitis. Complete recovery is the rule, but paralysis, aphasia and other sequels may occasionally be noted. Facial paralysis has been reported.

Respiratory Tract.—Inflammatory conditions of all parts of the respiratory tract occur, such as coryza, bronchitis, congestion of the lungs, and lobar or bronchopneumonia. Œdema of the glottis may be a dangerous complication.

Cardiac.—Following the attack there may be a slow or intermittent pulse and with this a low temperature and syncope. Endocarditis and pericarditis are rare.

Renal.—Acute nephritis generally ending in recovery may be noted and occasionally chronic nephritis follows an attack of mumps. It generally appears early in convalesence but it may be four or five weeks

after the attack before it manifests itself. Acute symptoms referable to the kidneys have been noted coming on with the onset of the swelling of the salivary glands.

Joint Symptoms.—Occasionally there may be pain or swelling of the joints and bursæ. Septic arthritis with suppuration has been reported, but should lead to a doubt as to the correctness of the diagnosis.

Blood.—Pick reports the blood findings in mumps to be a slight relative increase in the mononuclears at the height of the disease, but no leukocytosis.

Diagnosis.—This is as a rule easy—the history of exposure, with a large swelling, the centre of which is the tip of the lobe of the ear, usually suffices. It is differentiated from enlarged lymphatic glands by the position of the swelling, as in mumps the little hollow between the mastoid and the jaws is completely filled, while in adenitis the swollen gland is lower down. Non-specific parotitis frequently suppurates, especially if it occurs in pyemia.

Other Forms of Parotitis.—One should bear in mind that swelling and tenderness of the parotid may occur from numerous causes other than mumps. These non-specific enlargements may be classified as follows:

(*a*) Following or during infectious diseases. Typhus fever, typhoid, pneumonia, scarlet fever, and diphtheria, may be especially mentioned; but swelling of the gland may occur in any infectious disease and suppuration is very common. It is not very rare with syphilis.

(*b*) From septic infections, most commonly after pelvic and peritoneal inflammations, appendicitis, cystitis, and pyelonephritis. In these cases the affection may be sympathetic or due to infection.

(*c*) Following disease or injury of the abdominal or pelvic organs, and rarely from operations upon other parts of the body. The submaxillary and sublingual glands may also be affected. Bucknall gives the following list of operations which have been followed by parotitis, even though the operation was entirely aseptic: Exploratory laparotomy, gastrotomy, and other operations upon the stomach; enterectomy, colotomy; hernia operations; ovariotomy; operations upon the uterus and tubes; renal operations; operations on the liver and gall-bladder. To this list may be added castration, or operations on or injuries of the testes, the insertion of a pessary, the passage of a catheter, excision of hemorrhoids, and amputation of the leg. Delivery, abortion, menopause, or disorders of menstruation may be followed by parotitis.

(*d*) In chronic diseases, as diabetes, and any grave form of asthenia, and in the general paralysis of the insane. Symmes has called attention to chronic bilateral parotitis occurring in the insane, and reports five cases, all over thirty years of age. Three of these patients had syphilis.

(*e*) In chronic poisoning, as that due to mercury, lead, or the iodides.

(*f*) In association with facial paralysis, as in the case reported by Gowers.

(*g*) In Mickulicz's disease, in which there is enlargement of the salivary and lacrymal glands, coming on without any apparent cause.

(*h*) In gaseous tumors of Steno's duct such as are seen in glass-blowers and musicians.

Prognosis.—As a rule this is good. Occasionally one of the complications leaves a permanent lesion behind it; deafness is one of the most frequent of these. Suppuration rarely occurs. The cases in which suppuration and gangrene have been reported are either not mumps or are due to accidental infections. Stewart has reported a death from syncope on the fifth day, previous to which the breathing has been asthmatic. Atrophy or a lack of development of the testicle may follow orchitis. This is usually only upon one side, but it may in some instances be bilateral. In these latter virility is usually retained.

Treatment.—Mumps is a self-limited disease, little influenced by treatment. Much can be done, however, to make the patient more comfortable and to relieve pain. The food should be liquid, or soft, so that it may be easily swallowed without mastication. Acids and highly seasoned foods should be avoided. A mouth wash should be used to keep the mouth clean, as brushing the teeth may be impossible. The external application of heat is grateful to many patients. The swelling should be anointed with an ointment or a glycerin application to render the stretching of the skin less disagreeable. Various medicaments are mixed with these. Five per cent. guaiacol in an ointment, or glycerin may be used. Belladonna is highly recommended. Methyl salicylate may be applied to the gland three or four times a day. Internally a dose of calomel or a saline should be given at the onset, and the bowels kept open during the attack. Anodynes may be given if necessary. Tonics, especially iron, may be used during convalescence.

CHAPTER XXVII

TYPHUS FEVER

By THOMAS McCRAE, M.D.

Definition.—Typhus fever is an acute disease, occurring in epidemics or sporadically, characterized by a sudden onset, high fever, a macular-papular eruption, toxemia, and a comparatively definite course usually terminating by crisis. The cause of the disease is unknown but it is conveyed by the body louse and perhaps also by the head louse. The disease has been known by many names, hospital fever, fail fever, camp fever, ship fever, spotted fever, etc.

The work of recent years has added materially to our knowledge of the disease and many of the accepted views regarding it have to be revised. This has resulted from the important clinical observations of N. E. Brill and the experimental work of several observers, notably Anderson and Goldberger. We have learned that the disease is more widespread than was thought and that with singular complacency many of us have been looking at it without seeing it. It occurs quite frequently in the eastern cities of the United States and probably is commoner than we even now realize. This mild sporadic form with a low mortality is comparable to the mild forms of smallpox so prevalent at present. Experimental work has shown that the disease can be transmitted to monkeys, that the form described by Brill is identical with Mexican typhus, and that the infection is carried by lice. This last observation explains many puzzling features; for example, the decrease of the danger of infection when the patient was removed to a hospital and the great danger to attendants in epidemics, points to which Murchison drew attention. The conveyance of the disease by the body louse has been definitely proved by the infection of monkeys, and it seems probable that the head louse may also act as a carrier (Anderson and Goldberger[1]). The virus is not very resistant and the weight of evidence is against its being filterable.

At the present time epidemics of the disease are rare, but sporadic cases are certainly common in the eastern part of the United States. It is a disease rather of temperate and cold climates; Great Britain, Ireland, and Russia have suffered especially from it. How many unrecognized cases occur it is impossible to say. The disease is more or less endemic in Great Britain and Ireland, but it is well controlled and there is no danger to the community. It is comparatively frequent in Mexico. In certain parts of Europe, especially the southeast, the disease smoulders, and in certain of the Baltic and Polish provinces, in Hungary and Turkey,

[1] Reprint from *Public Health Reports*, No. 74, 1912; *Jour. Amer. Med. Assoc.*, 1912, lix, 514.

it is always more or less present. Southern Italy is also a focus and in northern Africa it is apparently endemic.

Etiology.—Various organisms have been described but none can be regarded as proved to be causal. There are varying opinions as to the time of greatest infection, many of the English writers holding that the danger of contagion is slight during the first week, while Curschmann believes that it is greatest at the beginning and height of the febrile stage. The virus is apparently present in the blood during the entire febrile period and for a day or two afterward in the experimental cases in monkeys.

Sex and Age.—In widespread epidemics the two sexes are equally attacked, but in districts where the disease exists for some time in partial epidemic form, males are in the majority. Pregnancy and lactation do not seem to have any special influence. Infants are apparently only slightly susceptible but after the age of five years children appear to be almost as much so as adults. The number of adults over fifty years is comparatively large. Among 7741 cases (Curschmann) there were 12.8 per cent. below fifteen years, 65.2 per cent. from fifteen to forty, 18.7 per cent. from forty to sixty, and 3.2 per cent. over sixty years of age.

Social Conditions.—These play a most important part and those living in unsanitary and crowded dwellings are most likely to be infected. Knowing the method of conveyance the reason for this is evident and also for the association of the disease with privation and poverty. It may be also that alcoholics and those who are poorly nourished are more easily infected.

Morbid Anatomy.—The findings after death are not characteristic, except in cases in which the typical rash can be made out. The condition is such as may be observed after death from an acute infection and knowing nothing of the history of the subject, it would be very difficult to make a diagnosis of typhus fever unless the rash was present. The absence of any definite lesions may be the most marked evidence of typhus fever. Rigor mortis is usually slight and disappears rapidly. Putrefaction occurs rapidly. There are often numerous areas of discoloration over the surface, and if the eruption was present the petechiæ and hemorrhagic areas may be seen. The blood is usually darker and more fluid than normal. The muscles are soft and on section have a deep red color, with hemorrhages into their substance in some cases. Histologically they show marked degeneration, which may be especially marked in the heart muscle.

The Nervous System.—The changes here are comparatively slight. There may be marked hyperemia of the membranes and occasionally hemorrhages, which are much more frequent into the membranes than into the brain substance.

The Respiratory Tract.—This shows changes very frequently. The mucous membrane of the pharynx and larynx commonly shows an inflammatory condition with perhaps superficial erosions. In some instances the changes about the pharynx are quite marked and at times perichondritis with necrosis and pus formation is seen. In the trachea

and bronchi the mucous membrane is inflamed and at times shows hemorrhages. With the bronchitis there is frequently some bronchopneumonia and collapse, while hypostatic congestion at the bases is common. Lobar pneumonia varies in different epidemics; Curschmann notes that in Berlin it was present in 15 per cent. of the fatal cases.

The Circulatory System.—The heart very commonly shows a certain amount of dilatation associated with degenerative changes in the muscle.

The Digestive Tract.—There may be excoriation and fissures in the tongue with ulceration of the gums. The mucous membrane of the stomach and intestine usually shows a catarrhal condition and ecchymoses may occur. There is no change in the Peyer's patches, although in some cases the follicles in the intestine may show some swelling. The mesenteric, glands are not enlarged. Ecchymoses may be found on the peritoneum. The liver may be enlarged, soft, and hyperemic and often shows signs of cloudy swelling.

The Spleen.—The condition of the spleen depends on the day of disease when death occurred. If this has been during the first week, the spleen is usually found enlarged, but afte the middle of the second week this is usually not found. On section the spleen is dark red and the pulp is soft.

The Genito-urinary Organs.—The kidneys are usually swollen, hyperemic, and show cloudy swelling. Acute nephritis is fairly common.

Symptoms.—Incubation.—This is usually considered to be between eight and twelve days but limits of four to fourteen days have been observed. The instances given of very short incubation periods are doubtful. During this period there may be general malaise, slight headache, and anorexia.

Onset.—This, as a rule, is abrupt, with headache, general pains, and frequently one or more chills or occasionally chilly sensations only. With the sudden onset there is usually high fever and great prostration, often so marked that it is rare to see a patient who has kept about longer than the second day, while the majority give up on the day of onset. The chill may be repeated and there may be nausea or vomiting. The general appearance at this early stage is often suggestive; the expression is dull and heavy with the face very red and the conjunctivæ showing marked congestion. The tongue is dry and tremulous. The temperature usually rises rapidly and may reach its maximum on the second or third day. With this there may be very severe headache but the patients rarely have much delirium, although they may show the ordinary febrile confusion. In severe attacks or in alcoholics there may be delirium almost from the onset. The abdomen shows no special features except that the spleen is generally enlarged very early.

About the third to the fifth day the eruption appears, first on the abdomen, then on the chest and shoulders, then over the back and extremities. The face becomes very much reddened and swollen but rarely shows the characteristic eruption and the palms of the hands and the soles of the feet usually escape. The rash usually requires from forty-eight to seventy-two hours for its full development. During this

period of the disease the patient usually shows very marked mental disturbances and the delirium is often of a violent type. The patient may be quiet or talk and gesticulate when he is excited. At this time he should be watched very carefully as he may jump out of bed and endeavor to escape or attack the attendants. During this period the eruption changes, a certain number of the spots becoming petechial, and with this the eruption becomes much more prominent and has a dirty, bluish color. If with this there be extensive subcutaneous hemorrhages, the skin assumes a curious dusky appearance, which is usually seen about the beginning of the second week. After this the picture changes somewhat, the patient becoming very weak, apathetic, and lying in stupor or coma vigil. There may be difficulty in swallowing and incontinence of urine and feces.

Throughout the attack the temperature continues high, being ordinarily about 104° to 105°. The pulse is usually frequent and toward the end of the attack becomes small and weak. In rare cases the rate is low, which is regarded as a grave sign. Toward the latter part of the second week, if the patient recovers, the fever disappears. Despite the usual description of the termination being by crisis, if the records are carefully examined it will be seen that in the majority the termination is by lysis and occupies about two days. A defervescence which lasts for four or five days should suggest some complication. Toward the end of the disease the enlargement of the spleen disappears and the skin lesions, with the exception of the petechiæ, disappear before the defervescence. The petechial lesions usually show desquamation and remain as brown or yellow spots. With the termination of the fever the skin becomes moist and there may be profuse sweating. Recovery is often very rapid.

Temperature.—This usually rises very rapidly, may be at 104° on the evening of the first day and reach the maximum on the evening of the second day. The remissions are usually slight and the curve shows little change until the latter part of the second week, when it begins to drop in the evening. In certain cases there may be a drop at the end of the first week but this is not constant. In the milder cases remissions may occur in the second week and occasionally precritical drops.

Defervescence.—This occurs usually from the twelfth to the fifteenth day, rarely being prolonged to the sixteenth or seventeenth. The temperature curve is much like that of the onset and may be with a very sudden drop of perhaps eight degrees in a few hours, but in the majority it occupies a period of about two days. In some cases with a comparatively mild course defervescence has been very protracted, or in mild cases the temperature may show many variations. Defervescence may occur about the end of the first week or be unduly prolonged. In certain of the fatal cases there is a very high temperature before death, while in others there is a fall to below normal, usually associated with a very rapid pulse and great prostration.

The Rash.—The study of this is most important, as on it in many cases the diagnosis must rest and it is practically the only characteristic sign. The eruption may appear from the second to the seventh day

but most commonly on the fourth or fifth, and this may vary in different epidemics. An erythematous rash has been described as occurring before the typical one. The eruption consists of two elements: (1) A rash much like that of measles, and (2) the characteristic petechial eruption. The first may appear before the roseola or with it and is especially likely to occur on the chest and abdomen, forearms and legs. It has been termed a mulberry rash and presents a dusky red mottling, which has been described as seeming to be below the surface of the skin. It may disappear before the end of the attack. The specific roseolous rash usually appears first on the abdomen and then about the chest and shoulders. After this it appears on the extremities, while the eruption on the trunk continues to increase in number. The whole rash is usually out within forty-eight hours and a second crop is practically unknown. The face rarely shows the eruption. The number of spots is very variable and bears no relation to the severity of the attack. As a rule three distinct stages may be observed: (1) A simple hyperemia; (2) a stage when hemorrhage is occurring into the eruption; and (3) typical petechiæ. The fresh spot is a pale red macule which disappears entirely on pressure and as a rule is not raised so much as the rose spot of typhoid fever. The color is usually pale, the outlines are more or less irregular and in dark-skinned individuals they may be very difficult to recognize. It is almost impossible to distinguish them by artificial light. The eruption may not develop beyond this stage but disappear entirely.

In the next stage the spots become darker, have a dirty reddish color, and do not disappear entirely on pressure. This is due to the deposition of blood pigment, which usually begins at the centre and extends to the periphery of each spot. The number of spots which undergo this transformation varies very much in different patients; there may be only a few or they may be so general that they give a curious appearance. These areas are often most numerous in the inguinal region and over the back. The hemorrhagic change must be distinguished from an additional petechial eruption, which is exactly comparable to what may occur in other infections. These petechiæ are likely to appear in the latter part of the disease and if abundant are of grave import. They are analogous to the hemorrhagic eruption which may occur in measles. Curschmann states that a slight hemorrhagic eruption in alcoholics is not important.

The duration of the hyperemic eruption is short. If there be no hemorrhagic change, the spots usually disappear by the second or third day, and if the hemorrhagic change is slight the spots persist for from four to six days. When the typical eruption is present the duration is usually from seven to ten days.

These are certain other conditions which are of interest. Among these is a miliary eruption, which may be present late in the attack and is of no special significance. As a rule distinct desquamation is seen after this but it may occur without the presence of sudamina. Herpes may be present and Curschmann noted them in 5 per cent. during one epidemic. Boils and bed-sores are not common. In severe attacks, particularly if there has been marked hemorrhage into the skin, there

may be areas of necrosis and sloughing. Gangrene has occurred in rare instances. Sweating may occur toward the crisis but is not often profuse.

The Nervous System.—The symptoms of involvement of the nervous system are due to toxemia, for organic changes are rare and the fever will not account for them, as in some patients they continue after this has disappeared. Headache is very common, almost constant early in the attack, and with it there may be vertigo and general pains. The psychical disturbances are interesting. At the onset the mental condition is usually clear, although the patients may be rather dull and show slow cerebration while insomnia is common. As the disease progresses the mental features become more marked in one of two ways—either violent delirium or a condition of marked apathy or almost coma. The delirium is of rather a violent type. The patients are usually very restless and may become violent, requiring to be watched very carefully. Thus one patient seen by the writer suddenly jumped out of bed, overpowered the orderly and put his fist through a strong wire screen over the window, cutting his arm severely. The appearance of the delirious typhus fever patients is often characteristic and in marked contrast to the delirious typhoid fever patients. They are curiously alert, seem to be watching what is going on around them, frequently try to get out of bed, and with the flushed face and bright eyes present a striking picture. The onset of severe delirium early in the disease is of bad omen. The other type is that in which coma predominates. The patients are much prostrated, lie quietly in coma vigil and take no note of their surroundings. With this there may be marked tremor, a rapid, feeble pulse, and in some instances the patient is practically in collapse. Coma may persist after the temperature is normal.

Tremor.—Tremor is one of the common severe manifestations and may be only slight or so general and severe that it suggests a convulsion. Subsultus tendinum with picking at the bedclothes is common. Actual convulsions have been noted. Naturally these severe nervous manifestations are associated with a grave prognosis. Sensory disturbances are sometimes troublesome at the onset and may occur in convalescence.

Organic changes in the nervous system are not common, although meningitis has been reported. Hemiplegia has occurred but is rare and is due to meningeal hemorrhage or to embolism or thrombosis, Neuritis may occur but is evidently not common.

Special Senses.—The characteristic appearance of the eyes due to the injection of the conjunctivæ has been noted. Hemorrhages into the conjunctivæ may occur and in some patients with marked coma vigil there may be ulceration. Disturbances in hearing are not uncommon and apparently largely due to hyperemia; otitis media may occur.

The Respiratory Organs.—Epistaxis has been noted early in the disease. A catarrhal condition of the nose and pharynx is very common at the onset, frequently extends down the trachea and bronchi, and sets up an irritative cough with which there may be very little expectoration. In a certain number of cases more serious changes may occur, such as erosions, fissures, extensive ulceration, and œdema. These conditions

are always of grave import, both on account of the local condition and the danger of pulmonary infection, while, should the patient recover, permanent changes in the larynx are common. In the lungs there may be bronchopneumonia, hypostatic congestion, or lobar pneumonia, all of which are serious. Pleurisy occurs not infrequently and if with pneumonia, empyema may follow.

The Circulatory System.—The changes here show no special peculiarity. With the toxemia there may be myocarditis and some dilatation. The pulse early in the disease is usually rapid, small, and of low tension. In the second week the pulse becomes small and at times irregular. A slow pulse rate is occasionally seen. The heart sounds show considerable change, the first becoming much like the second and later in the attack disappearing entirely.

Leukocytosis generally occurs. Love reports the average for 26 cases as 24,000, with an increase specially in the polymorphonuclear cells. He noted that in the blood of the fatal cases no eosinophiles were present but they were never completely absent in the blood of the non-fatal ones and considers that the absence of eosinophiles does not necessarily mean that death follows but does mean a grave prognosis. In the non-fatal cases there was usually a slight increase in the large mononuclear elements. There was usually an increase in the leukocytes after the appearance of the eruption. In 4 cases in the Johns Hopkins Hospital there was leukocytosis in all, the average of the highest counts being 22,000. The highest count of 32,000 was shortly before death in a patient who at death had a normal temperature.

The Digestive Tract.—The tongue is usually furred, and as the disease progresses, it and the lips are likely to become fissured and covered with sordes. Gastric disturbances do not often occur. The bowels are usually constipated, although there may be diarrhœa. If the rash be of marked hemorrhagic type it is quite possible that there may be hemorrhage into the intestine, but such cases are rare. Jaundice has been noted during the second week, and is probably toxic.

The Genito-urinary Organs.—Changes in the kidney are such as may occur in any acute febrile disease and albuminuria is common, usually appearing about the third or fourth day and lasting until defervescence. In rare cases there may be a definite nephritis, which is always serious. Orchitis is rare. Menstruation is usually suspended during the attack, although occasionally it may occur with the onset. Pregnancy does not afford any protection against the disease, but the danger of abortion is probably less than in any other severe acute disease and it is less likely to occur during the later months of pregnancy.

Variations in the Disease.—There may be great variation from the usual course, as is true of all acute infections. In some patients the attack is so short that the recognition offers great difficulty. Curschmann describes a group of abortive cases which begin with severe symptoms, the temperature being high at first and then falling rapidly. Somewhat like these is a group of cases seen especially in physicians and nurses who are handling patients with the disease, in whom there are symptoms suggestive of a slight toxemia. They usually recover quickly as soon

as they are removed from contact with the patients. Malignant attacks are seen, especially in epidemics, with death on the second or third day Hemorrhagic cases occur as in the other acute infections.

The mild form prevalent in the United States differs somewhat from the severe epidemic form and it is important to know its characteristics. We are indebted to Brill[1] for a complete description of its features. The onset is usually sudden with a chill or chilly sensations, followed by severe headache and general pains. Fever appears quickly, reaches the maximum by the third day and is fairly constant (usually 103° to 104° F.). Prostration and apathy are marked. The eruption appears on the fifth or sixth day, is usually profuse on the body and extremities and comes out in one crop within a period of twenty-four hours. It is a macular-papular rash of an erythematous character, dull red in color, occasionally petechial, and usually not entirely obliterated by pressure. It persists until the end of the attack. It may easily be regarded as an unusually profuse, bright typhoid fever rash.

During the height of the attack the patient is quiet, looks ill, has a flushed face and congested eyes, and suffers from severe headache. Bronchitis is fairly common. The pulse is full and not as rapid as might be expected from the fever. The tongue is coated; constipation is the rule; the spleen is usually enlarged. There is slight leukocytosis (9000 to 11,000). Blood cultures are negative. The termination is usually by crisis after a duration of twelve to fourteen days. The mortality is very low.

Relapse.—This is exceedingly rare and for ordinary purposes the probability of its occurrence may be disregarded. Among 18,268 cases in the London Fever Hospitals there was only 1 case of relapse.

Association with Other Diseases.—There are rare instances in which typhus fever coexists with one of the acute exanthemata, but some of these may be instances of the rapid succession of one infection after the other. A point of interest is the possibility of typhoid and typhus fevers occurring together. There are instances of a patient with typhoid fever being sent by mistake into a typhus ward and contracting the disease. Diphtheria may coexist, but in the absence of definite bacteriological findings the diagnosis is doubtful, owing to the frequent occurrence of membrane over the pharynx in typhus fever. Relapsing fever and typhus fever have been noted as coexisting. Curschmann considers that chronic alcoholics are prone to contract the disease and that the course is usually more severe, as they are apt to show severe nervous manifestations, while cardiac failure and renal changes are common.

Convalescence.—This is usually rapid and the patients are often hungry soon after the temperature becomes normal. As a rule the nervous symptoms disappear with defervescence, although delirium or mental confusion may persist for a few days. True psychoses are rare. Subnormal temperature is very commonly present during the first week of convalescence and the pulse may continue rapid; bradycardia sometimes occurs. Neuralgia is said to be fairly common.

[1] *Amer. Jour. Med. Sci.*, 1910, cxxxix, 484; and 1911, cxlii, 196.

Prognosis.—In slight epidemics the death-rate may not be higher than 10 or 15 per cent., while under unhygienic conditions it may rise to 20, 30, or 50 per cent. In hospitals during epidemics the average mortality is from 20 to 25 per cent. Murchison's series of 18,592 cases showed a mortality of 18.78 per cent. In the American cases the death-rate is very low, about 1 per cent. The effect of age is marked; thus in children below the age of five years the death-rate is high but from ten to fifteen years is low, while over the age of fifty it is high. The position in life influences the mortality, for those who have been living under poor conditions of sanitation or in crowded surroundings are more likely to die. Alcoholism is a serious feature in the prognosis. The influence of overexertion is of interest, for in epidemics a large proportion of the physicians, nurses, and attendants who take the disease die of it. The conditions under which the patients are treated influence the mortality. The death-rate is lower if they can be removed from unsanitary surroundings to a good hospital.

The form of severe infection spoken of as *typhus siderans* is almost always fatal, death occurring by the third or fourth day and perhaps even before the rash is completely out. The hemorrhagic form usually ends fatally, although if the hemorrhagic process makes its appearance late, the prognosis is more favorable the later it appears. With hyperpyrexia the prognosis is usually grave, although a high temperature early in the attack is not of especially bad omen but its persistence is serious. The condition of the circulation is important, the pulse is rapid early in the disease, as a rule, but if with this it be soft and easily compressible or irregular, the outlook is grave. The appearance of pulmonary complications is serious, especially in the older patients, and with extensive bronchitis there is always the danger of bronchopneumonia. A diminished amount of urine, the presence of very large amounts of albumin and especially the onset of an acute nephritis are of serious import. The early onset of severe nervous manifestations is a grave matter, while coma vigil with much muscular tremor means severe intoxication.

Diagnosis.—In an epidemic this is likely to offer comparatively little difficulty, but when cases arise sporadically, it is well to remember that immediate recognition may be very difficult, as is likely to be true of any acute infection which the profession has had little opportunity of seeing. The mistake of considering other disease to be typhus fever is most likely to be made during epidemics; with sporadic cases or the early ones of an epidemic we are more likely to make the opposite error and mistake typhus fever for some other disease.

Diagnosis at Onset.—The onset may offer points of resemblance to several of the acute exanthemata, especially smallpox, scarlet fever, and measles. Relapsing fever, meningitis, and septicemia may also give difficulty. In the acute exanthemata we may have the same sudden onset with a rapidly rising fever, severe headache and marked prostration, and until the eruption appears it may be impossible to make the diagnosis. In the recognition of smallpox, the occasional, early scarlatiniform rash is important, while the characteristic rash of smallpox usually occurs on the face early in the attack, while in typhus fever

the face is usually not involved. The drop in temperature with the appearance of the rash in smallpox may be of assistance. There may be special difficulty in the differentiation of the hemorrhagic form, as it may end fatally before the characteristic rash appears. There may be the same difficulty in distinguishing the disease from scarlet fever or measles. The characteristic appearance of the tongue, on which so much stress is laid by McCollom, may be of help as regards the former, while the early coryza, bronchitis, and Koplik's spots would assist in the recognition of measles. In any doubtful case care should be exercised before a positive diagnosis is made and in certain instances it is necessary to wait.

Relapsing fever may cause difficulty, especially as the diseases arise under the same conditions, but examination of the blood and the subsequent course should make the diagnosis clear in a very short time. The coexistence of the diseases has to be kept in mind. Cerebrospinal meningitis may suggest typhus fever, especially if there be a rash with it, but the result of lumbar puncture will usually render its diagnosis clear. Septicemia, and especially the type with a latent endocarditis, may give great difficulty. The result of blood-cultures may be positive, but in some cases it will probably be necessary to observe the patients for several days before a positive diagnosis can be made. Plague may give difficulty and also perhaps pneumonia at an early stage. Malarial fever, certain forms of purpura and typhoid fever with a sudden onset may all give difficulty but careful examinations and continued observation should soon give the diagnosis. Uremia, probably with a severe terminal infection, has also been confused with this disease. It seems reasonable to conclude that with a sporadic case of typhus fever the diagnosis before the appearance of the rash will be most difficult and can rarely be made with any certainty.

Diagnosis in the Stage of Eruption.—In typical cases this is not likely to offer much difficulty, which is true of disease generally, as it is the atypical cases that give the difficulty and for them no definite rules can be given. The diseases which have to be especially considered are typhoid fever, measles, purpura, and some of the other acute infections. It must be kept in mind that the rash of typhus fever may show great variation from the usual descriptions, and it is such cases that offer the greatest difficulty in diagnosis from typhoid fever. This is particularly true of the sporadic form in the United States. The onset of typhoid fever is usually more gradual, the early symptoms very much less severe, and it is rare to have severe nervous manifestations early in the course. Prostration occurs early in typhus fever. The pulse in typhus fever is much more rapid early in the disease and is rarely dicrotic. The enlargement of the spleen is common to the two diseases but appears early and disappears early in typhus fever. As a rule there is no leukocytosis in typhoid fever and the result of blood cultures, the ophthalmo-reaction, or the Widal test may make the diagnosis positive. The eruption in typhus fever is usually at first only hyperemic and not hemorrhagic and the number of areas that become hemorrhagic may be few, while on the other hand a certain number of the rose spots in

typhoid fever may become hemorrhagic. The typhus rash is common on the arms and legs which is rare in typhoid fever. The rash of typhus fever appears much earlier than that of typhoid fever and in one crop, while in typhoid fever the rash appears in successive crops. Then in typhus fever the eruption is fairly even over the body and extremities. The general appearance of the patient is often suggestive. The curious wild look with swollen, red face and injected eyes (sometimes termed the "ferret eyes") of the typhus patient is in contrast to the ordinary dull, stupid appearance of the one with typhoid fever.

The rash of measles, especially early in the attack, may be much like that of typhus fever, and if in the latter disease the measles-like eruption, sometimes present, is marked, there may be great difficulty in the diagnosis. The face is generally attacked first in measles, while as a rule it escapes in typhus fever. The appearance of petechiæ should make the diagnosis clear. Careful examination should always be made for Koplik's spots. In measles with the appearance of the eruption there is usually a drop in the temperature, which does not occur in typhus fever.

Purpura is not likely to give difficulty for any length of time. The occurrence of insect bites in patients who are suffering from fever may cause difficulty, but careful examination of the lesions will probably show the mark of the bite in the centre. A copaiba rash has been mistaken for that of typhus fever. Anthrax and glanders have given difficulty in rare instances.

Prophylaxis.—Wherever possible the patients should be removed to hospitals. In case of an epidemic it is best to treat the patients in temporary barracks or in tents. It is important in epidemics to carry out periodical careful inspection of crowded districts and unsanitary localities, so that cases may be recognized early, and isolated. Knowing the method of transmission every effort should be made to kill the lice which may have been infected. All the patient's clothing should be boiled, sterilized by heat or burned, and the room thoroughly cleaned. The hair of the head should be clipped close or shaved, and the head washed with carbolic acid solution (4 per cent.). It would be advisable to give the patient a sponge bath with carbolic solution (2 per cent.). Those with the patient before he is cleaned should be careful to avoid contact. Those living with the patient should receive thorough treatment for pediculosis and all their clothing should be sterilized by heat, boiling, or by carbolic acid solution (5 per cent.).

Treatment.—We have no specific treatment. We have to deal with a severe toxemia and with certain complications, especially of the respiratory tract and circulatory system, which are to a considerable degree secondary to the toxemia. Consequently our endeavor must be to keep the patient in the best possible condition, nourish him as well as we are able and favor the elimination of toxins. The patients should be put to bed at once and kept absolutely at rest. The diet should be fluid; milk and its modifications, albumin water, broths and eggs may all be given. It is probably well to feed at frequent, regular intervals, and care should always be taken with those who are dull and stupid that food

does not pass down into the respiratory tract. Large amounts of water should be given and the endeavor made to increase the urine to several liters a day. The administration of alcohol should be governed by the condition, for with marked toxemia and great prostration alcohol is useful, probably best as whisky.

Hydrotherapy, if possible in the form of the tub bath, should be carried out as in typhoid fever. In severe attacks it is well to give the tubs at a temperature of 70° F. In the patients with marked nervous symptoms it is well to use cold affusions to the head during the baths and an ice-bag or cold cloth should be kept constantly applied at other times. The use of antipyretic drugs does not seem wise. Delirium may require treatment, and while the baths are usually the best means of combating this, it is sometimes difficult to give them. In this event one may have to substitute packs or sponges. Delirious patients should be constantly watched. With marked delirium, severe headache, or insomnia, it may be well to give bromides and opium, but in severe cases it is better to use morphine hypodermically. Careful attention should be paid to the condition of the nose and mouth and they may be irrigated or washed with an alkaline antiseptic solution. If signs of laryngeal involvement appear, the patient should be carefully watched so that if œdema of the glottis comes on, it may be recognized at once and tracheotomy done. The patients should be kept turned from side to side as much as possible to lessen the danger of hypostatic congestion. If there be failure of the circulation, strychinine may be given hypodermically (gr. $\frac{1}{40}$ to $\frac{1}{20}$, gm. 0.0015 to 0.003), digitalis, perhaps best in the form of digitaline hypodermically (gr. $\frac{1}{30}$, gm. 0.002), and camphor hypodermically (gr. ij, gm. 0.13), every two to four hours. Caffeine is also recommended. Conditions in the other organs must be treated as they arise. The bowels should be kept open by simple purgatives.

Convalescence is usually rapid, but it is probably wise to keep the patient in bed for a week after the temperature is normal. If the pulse continues rapid or very slow, great caution is advisable and the patient should be kept quiet for some time, as in such cases there is always the danger of syncope.

CHAPTER XXVIII

YELLOW FEVER

By the Late JAMES CARROLL, M.D.

REVISED BY

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Synonyms.—Yellow Jack, Bilious Remittent Yellow Fever, Hemagastric Pestilence, Black Vomit, Gibraltar Fever, Barcelona Fever, Fièvre Jaune, Gelbes Fieber, el Vomito, Fiebre Amarilla, Typhus Icterodes, Pestis Americana, Febris Maligna Biliosa, etc.

Definition.—An acute, specific, infectious disease, characterized by fever occurring occasionally in one, but generally in two, paroxysms; the first of these is of short duration and followed by a brief remission or intermission which is succeeded in turn by secondary fever, accompanied by albuminuria, jaundice, passive hemorrhages from the mucous membranes, and, in severe cases, black vomit.

Etiology.—From the time of Benjamin Rush the transmission of yellow fever through the atmosphere has been taught and believed; but such declarations were met with seeming proofs of its transmission by indirect contact, and by some it was held to be even directly contagious. English and Spanish physicians who had passed through large epidemics were about equally divided in opinion upon the subject, and this confusion continued for centuries. No matter to which side of the argument an authority might lean, facts and evidence were always forthcoming to show that his theory did not explain all the conditions to be encountered. For instance, persons who secluded themselves during an epidemic frequently became infected, while, on the other hand, many who were in constant attendance upon the sick in hospital escaped infection; and again, a single visit to the sick, and only one visit, was shown in many instances to be sufficient to insure an attack. The fact that certain buildings or localities, and vessels in particular, retained the infection during the warm season or in tropical regions, and the constancy with which the infection appeared to cling to the vicinity of water, led to the belief, and with reason, that it resulted from fermentation, the most favorable conditions for which require the presence of heat and moisture. The beginning of many epidemics could be traced to the presence of vessels recently arrived from the tropics, and as the holds of wooden vessels were nearly always in an offensive condition, the fermentation theory received strong support. After the discovery of bacteria as the cause of fermentation and putrefaction, as well as of disease, there seemed to be no longer any room for doubt. It was very difficult to explain why persons suffering with the disease

often failed to communicate it to others after having been removed only short distances.

It was shown that persons who contracted yellow fever on shore might be treated at a sufficient distance from the shore, on board vessels, without danger of communicating the disease to other persons on the same vessel. On the other hand, it was also well known that vessels frequently became infected while lying at ports where the disease prevailed; and these facts were hard to reconcile.

The first announcement of the discovery of a bacterium as the cause of yellow fever was made by Domingos Freire, of Rio de Janeiro, who, in 1883, described his *Cryptococcus zanthogenicus* and claimed that it was the specific cause of the disease. Carmonary Valle of Mexico, Charles Finlay of Havana, and Gibier of Paris, each thought that he had discovered the specific bacterial cause of the disease; but subsequent investigations by Sternberg showed that they had been mistaken. Sternberg himself, after several years of painstaking work, reported a negative result, and but little more was done in this direction until Guiseppe Sanarelli announced in 1897 that he had found and cultivated the causative agent, and that by means of inoculations with it and with its filtered products, respectively, he has produced the characteristic lesions of the disease in lower animals and the clinical phenomena in men. He named the organism that he had found *Bacillus icteroides*. Sternberg had obtained a bacillus by the use of the ordinary culture media, and found that it also proved to be quite pathogenic for lower animals. Because of his inability to establish its identity, he named it *Bacillus X*, and caused it to be preserved. Upon the publication of Sanarelli's results, Dr. (then Surgeon-General) Sternberg directed the late Major Walter Reed and the writer to undertake experimental work with Bacillus X, and later with *Bacillus icteroides*, for the purpose of comparison and identification. After working for several years it was concluded[1] that *Bacillus X* belonged to the colon group and *Bacillus icteroides* to the hog-cholera group and that the blood obtained from yellow fever patients exerted practically no agglutinative effect upon *Bacillus icteroides*. Although persistent efforts were made to sustain the claim of Sanarelli for *Bacillus icteroides*, the best European and American authorities now uphold the finding of the American Army Commission, that it was a secondary invader only.

In the year 1900, during the American occupation of Cuba, a commission composed of Drs. Walter Reed, James Carroll, Aristides Agramonte, and Jesse W. Lazear, of the United States Army, was formed on the Island of Cuba to investigate the subject of yellow fever. In a report published in the month of October of the same year they stated that they had been unable to find *Bacillus icteroides* in 29 cases, that *Bacillus icteroides* was not the cause of yellow fever, and that the mosquito served as the intermediary host for the parasite of the disease. After abandoning the search for *Bacillus icteroides* they decided to put the mosquito theory to the test, and for this purpose secured a number of

[1] Reed and Carroll, *Jour. Exper. Med.*, 1900, vol. v, No. 3.

volunteer subjects, among them two members of the commission, another contract surgeon named Pinto, and later, for other experiments, some soldiers and Spanish immigrants. Finlay had already claimed to have produced yellow fever with mosquitoes kept from two to six days after biting a patient, and the mosquito suggested by him was the one used in making the tests.[1] Experiments were begun by Dr. Lazear in the month of August, 1900, with mosquitoes kept from two to thirteen days after contamination, applying them to 9 individuals, without success; but in the 2 last cases, using the same mosquito kept twelve and sixteen days, respectively, the attempts were successful.[2] In September, Jesse W. Lazear, a member of the commission, knowingly permitted himself to be bitten again by a stray insect in a yellow fever hospital while he was applying other mosquitoes to patients. He was bitten on September 13th, sickened on the 18th, and died on the 25th, after he had succeeded in showing in two other persons that the mosquito could convey the infection. He obtained immediate confirmation of his first case by applying the same mosquito at once to a second individual, on the day that the writer was taken ill. This second case also proved positive within five days after inoculation.

In order to further confirm and perfect the results obtained by Lazear, an isolation camp was established two months later, and named in his honor Camp Lazear. In this camp there were placed two physicians. one an immune, the other a non-immune, with a number of soldiers and some Spanish immigrants, all of whom had expressed their willingness to submit to the experiments, and after a sufficient period of strict quarantine the following confirmatory tests were made: (1) Fifteen mosquitoes that had previously bitten patients with yellow fever were liberated in a mosquito-proof building especially constructed, and which had been divided by a wire-screen partition, extending from floor to ceiling, into two compartments, each of which was furnished with a bed that had been previously disinfected. The mosquitoes were liberated into one compartment and this was entered soon after by a non-immune, who, lying down upon the bed and exposing his chest and limbs, was bitten by several of the insects. He returned again for a short time on the same day, when he was again bitten by some of the insects, and on

[1] Dr. Charles Finlay (*Anales de la Academia de Ciencias Medicas de la Habana*, Habana, 1890–91, xxvii, 501), of Havana, was the first to propound clearly a mosquito theory of the transmission of yellow fever, though an insect theory which was made to include the mosquito especially, as well as certain other insects, was advanced and ably supported by Nott, of Mobile, Alabama, in 1847. In 1876, Dowell, of Galveston, Texas, again called attention to the fact that the gnat and mosquito were governed by the same natural laws as yellow fever. A number of observers had previously noted the unusual prevalence of mosquitoes during epidemics. Finlay attempted to prove his theory, but could not have succeeded because his mosquitoes were kept only two to five days (in one case six days) after biting a patient (Carroll, "The Transmission of Yellow Fever," *Journal of the American Medical Association*, May 23, 1903). The cases among his subjects were clearly the result of the great prevalence of the disease in Havana at the time, and his tests were made without the precautions necessary to guard against accidental infection.

[2] "The Etiology of Yellow Fever—A Preliminary Note," by Reed, Carroll, Agramonte, and Lazear. Proceedings of the American Public Health Association at the 28th Annual Meeting, Indianapolis, Ind., October, 1900.

the following morning several more attacked him when he entered the third time for only a few minutes. This man became ill with a typical attack of yellow fever on the fifth day after he first exposed himself to the mosquitoes. On the evening of the day that this subject first entered the mosquito compartment, two other non-immunes were admitted to the opposite section, where they slept for eighteen consecutive nights, separated from the mosquitoes only by the wire screen partition. Their health was not disturbed in the slightest degree by this exposure. (2) Another mosquito-proof house was constructed and supplied with several boxes of soiled articles of bedding and clothing direct from the yellow fever hospital in the city. These articles had been intentionally soiled with urine, fecal matter, and black vomit obtained from fatal and other cases of yellow fever. This house was entered for twenty-one consecutive nights by two soldiers and a contract surgeon, non-immunes, who, after unpacking the boxes, handled and shook the soiled articles, hung them upon nails in the walls, and then retired for the night. In the morning upon rising they removed the garments from the walls, handled them again, then folded them and replaced them in the boxes. This was continued daily; the individuals remained in strict quarantine and were confined to the camp, but were permitted to spend the day-time in a tent set apart for the purpose, every night during the experiment being passed within the house and in the manner mentioned. At the end of three weeks this party was relieved and another party consisting of two non-immunes occupied the house in the same way, after the addition of a fresh supply of contaminated articles received from the hospital. They repeated the unpacking, handling, and repacking the soiled articles for twenty-one nights and none were infected. Newly soiled articles of bedding and clothing had been added from time to time, and after the receipt of another supply upon their release, two additional non-immunes slept in the house for twenty-one nights longer. These men passed their nights within the identical garments and between the same sheets that had been used by patients dying of yellow fever. One of them slept with his head upon a towel soiled with blood drawn from a patient in the first day of the disease, and which was shown by inoculation to be capable of infecting. These men also came out of the experiment building in perfect health, and had increased in weight. The majority of the men thus exposed were afterward inoculated by means of mosquitoes or by blood injections, and their susceptibility was proved by their becoming infected. This was deemed sufficient to show that susceptible persons might live and sleep in intimate contact with fomites from yellow fever patients and suffer no harm as long as they were not bitten by contaminated mosquitoes. (3) Men were singled out in certain tents within the camp, and to these contaminated mosquitoes, that had been kept sufficiently long, were applied, with the result that many contracted the disease. In every case the attacks followed within the usual period of incubation, and no other persons in the camp became infected than those purposely inoculated. Every precaution was taken, a strict quarantine was maintained, and the residents of the camp were required to sleep always beneath mosquito

netting. It was shown by these experiments that mosquitoes were capable of communicating the infection as long as fifty-seven days after they had bitten a patient suffering with yellow fever. (4) It was further demonstrated that the subcutaneous injection into a non-immune of 2 cc., 1.5 cc., 1 cc., or 0.5 cc., of blood drawn directly from the vein of a yellow fever patient in the first or second day of the disease would promptly cause an attack of yellow fever.

In the beginning twelve attempts at inoculation with mosquitoes which has been kept from four to eighteen days after biting the patient all resulted in failure; but the insects used for these tests had been kept at room temperature during the months of November and December. In January there was another failure resulting from the application of twelve mosquitoes kept for twenty-two days at a temperature of 82° F. after they had bitten a very mild case in the eighth hour of his attack. Yet ten persons in all were infected by the application of mosquitoes during the winter, and the other experiments showed conclusively that fomites cannot transmit the disease; that yellow fever can be communicated by means of blood injections; that an infected house is simply one that contains "ripe" infected mosquitoes; and that the mosquito is harmless until twelve days or longer after it has bitten a patient, but that it retains the power to infect as long as it lives.

The first to confirm the efficiency of the mosquito as the transmitting agent of yellow fever was John Guiteras, of Havana, who, in the spring of 1901, succeeded in infecting a non-immune Spaniard by applying to him a contaminated mosquito. In August of the same year Guiteras again succeeded in producing 7 additional cases, and immediately after this it was demonstrated independently by a member of the Army Board (Carroll) that the diluted blood serum from a patient suffering with yellow fever is capable of conveying the disease when injected subcutaneously in quantities of 1.5 cc. after having been passed through a new, sterilized Berkefeld filter. It was further shown that the blood of a patient could be deprived of its power to infect upon subcutaneous inoculation by previously subjecting it to a temperature of 55° C. for ten minutes.[1] In this work six additional experimental cases were produced, and all recovered, a total of twenty-two cases intentionally inoculated with yellow fever by the Army Board, without a death.

The doctrine of the transmission of yellow fever by the mosquito is now firmly established. Marchoux, Salimbeni and Simond, the members of the French Commission, concluded that yellow fever is contracted in no other way than through the bite of the mosquito *Stegomyia fasciata;* that to become capable of infecting, the mosquito must bite a patient during the first three days of the disease, and that the mosquito is harmless until the lapse of at least twelve days after biting a patient; that no other mosquito aids in the transmission of yellow fever; that simple contact with the patient, his personal effects, garments, or excreta, will not communicate the disease; that yellow fever can become epidemic only in places where the mosquito exists; and that prophylaxis against

[1] This experiment was repeated at Rio de Janeiro by the French Commission, who reduced the time of exposure at the same temperature to five minutes.

yellow fever rests entirely upon the means taken to prevent mosquitoes from biting the sick and the well.

In Mexico yellow fever has been eradicated from its endemic focus at Vera Cruz. In New Orleans during 1905 with an epidemic beginning earlier in the season than usual, with a larger non-immune population than ever before, and with the disease well established early in August, great success was attained in ultimately controlling and stamping out the epidemic before its disappearance could be attributed to the occurrence of frosts. Could the permanent endemic foci in Rio de Janerio and in some of the smaller Central American republics be once destroyed by intelligent and systematic efforts, the United States and Mexico would be freed from the danger of yellow fever, and concerted action by the countries concerned would make it an easy matter to insure the complete suppression of the disease and immunity for the future.

Notwithstanding all efforts the specific organism of yellow fever still awaits recognition. The arguments opposed to the idea that the invisible causative agent of yellow fever is a bacterium are: (1) It has never been recognized nor cultivated; (2) according to the French Commission the blood of a patient loses its power to infect within two days if exposed to the air, and within five days if air be excluded; (3) the absolutely non-contagious and even non-infectious character of the disease under conditions otherwise favorable but in the absence of the mosquito. The arguments in favor of its being a member of the animal kingdom are: (1) Its obligatory parasitic existence in man and the mosquito, alternately; (2) the necessity for the lapse of a definite period, two weeks or more after the ingestion of the blood, before the mosquito becomes capable of infecting; (3) the restriction of the hosts to a single vertebrate and a single genus of invertebrates which points to a definite cycle of development; (4) the rapidity of development of the parasite within its invertebrate host is governed by conditions of external temperature in the same way as the rate of development of the malarial parasite in the anopheles mosquito.

Susceptibility.—All races are not equally susceptible; the white races, and especially those with fair skins and who inhabit northern climes, appear to suffer most. The negro is susceptible but not in the same degree as members of the white races. One attack of the disease generally confers permanent immunity and second attacks are rare. It is quite possible that a person after recovering from a very mild attack would again become susceptible after a lapse of time. The incidence is greatest in young adult life, and the mortality rate is higher among those who are debilitated. The immunity enjoyed by the inhabitants of countries where the disease has become endemic probably results from mild infections during infancy and childhood.

Special Pathology.—Yellow fever is a general infection with severe intoxication. The most marked effect of the toxin is seen in the liver, the probable reason being that the toxin possesses a marked affinity for the hepatic cells. From the clinical manifestations we would infer also that there is some affinity between the toxin and the cells of the central nervous system and perhaps those of the muscular system in

general, as well as the vascular endothelium. The lesions in the digestive tract are chiefly mechanical and secondary to those in the liver; it is difficult to say to what extent the lesions in the kidney are due to the toxin and how much to secondary intoxication resulting from damage to the liver.

Rigor mortis appears early and is very marked. When death takes place on the eigth or ninth day, the skin of the trunk is usually of a canary-yellow color. This is less intense on the extremities, but the eyeballs are deeply tinted and the face is distinctly yellow. The intensity of the color varies usually with the stage and severity of the attack. The dependent parts of the body are deeply discolored and livid, and the same is true of the tips of the fingers and toes, scrotum, penis, etc. Hemorrhages beneath any or all of the serous membranes are frequent. No constant lesions are found in the brain and spinal cord. The vessels are usually engorged, and hemorrhages frequently take place into the brain substance and beneath the membranes.

The lungs are the seat of marked hypostatic congestion, with hemorrhage; and hemorrhages are often visible beneath the pleural membrane. The heart is distended; its muscular tissue is of a deep reddish-brown color and sometimes softened in consistency, but this is not constant.

Digestive Tract.—The stomach may be found distended with black, fluid blood, even in cases in which black vomit did not appear during life. After removing and washing the stomach, its mucous membrane may be found pale and eroded, or blood stained. At the pyloric end there is congestion of its mucosa, as a rule, and there may also be found large areas of diffused submucous hemorrhage.

The mucous membrane of the duodenum is always deeply congested, swollen, and the seat of hemorrhages. The condition of the jejunum and ileum depends upon the duration and severity of the attack. The upper part of the jejunum is usually involved with the duodenum, and the congestion may continue for some distance into the ileum. On the other hand, the ileum may appear practically free from any pathological lesion after the contained blood has been removed. The passive damming up of blood in the mesentery and intestine, which results from compression of the capillaries by the swollen liver cells, is manifested earliest and with the greatest intensity in the pylorus and duodenum. Passive congestion is always more marked in this region (duodenum) than lower down, and may be regarded as invariably accompanying the disease. This is probably the explanation of the tenderness on deep pressure in the epigastrium.

The liver is tense, firm, and smooth; the color is variable. It may be uniform or mottled but is always yellowish or brownish and usually shows areas of congestion or hemorrhages beneath the capsule. Upon section the organ is firm, pale, and friable. There is a remarkable alteration in the normal arrangement of the liver cells; in general they show marked variations in size and their normal outlines are distorted. The majority are densely packed with medium-sized fat droplets, and the protoplasm of some is coarsely granular. The degree of fatty degeneration is variable, but it is always present in remarkable degree;

in certain instances practically all the lobules are affected throughout while in others whole lobules or small areas may escape. The jaundice, which results from the pressure of the swollen liver cells upon the smaller biliary vessels, is, of course, hepatogenous and not hematogenous.

In the excessively degenerated condition of the liver in the advanced stages of severe attacks but little urea can be formed, and the carbonate, carbamate, and lactate of ammonium, being no longer converted by the liver into urea, are retained in the circulation and act as poisons. There are thus produced two serious complication, anuria and ammonemia. Urea is deficient in the urine in yellow fever, and this occurs because the liver no longer provides the normal quantity. The delirium and coma (with or without convulsions) seen in fatal cases are due to ammonemia and not to uremia, and by the early elimination of toxin we lessen the degree of fatty degeneration of the liver and diminish the tendency to anuria, to severe intestinal hemorrhages, and to the ammonemic intoxication which is superadded in the fatal cares.

Kidneys.—The condition of the kidneys is more variable than that of the liver because involvement of these organs is not so general or so intense. In the fresh condition the kidney is of normal size or slightly swollen, pale, and fatty, or congested. In sections there is usually found a condition of acute diffuse nephritis; the lesion is sometimes of a distinctly degenerative type; at others it consists of not much more than a well-marked cloudy swelling. The glomeruli may be swollen and engorged or atrophied; the capsular epithelium may have suffered but little change, or it may have become swollen or degenerated, or have entirely diappeared.

Spleen.—The spleen may or may not be enlarged and soft, but it is always congested. The swelling, when present, is probably due to the presence of bacteria as secondary invaders.

The old idea that the blood undegoes degenerative changes in yellow fever is without foundation. In the later stages many of the leukocytes may contain minute fat droplets or vacuoles, and there may be some anemia; but in the early stage there is no marked anemia, no cell destruction, and the leukocytes are practically normal in number and appearance. In a small proportion of the cases a moderate degree of polymorphonuclear leukocytosis can be demonstrated.

Symptoms.—The earliest symptoms may be a premonitory feeling of malaise, with pain in the back and loins, or a slight frontal headache There is usually a furred tongue, with constipation. In the majority no marked premonitory symptoms are noted.

At the onset there may be a sudden chill or rigor occurring at night or during the day. The patient may have lost his appetite and have gone to bed to rest and sleep in the middle of the day, to wake up later with high fever. With the onset of fever there is a sharp headache, generally frontal, but occasionally occipital in location; the face is flushed, the eyes injected, rachialgia is often present, and the temperature may range anywhere from 102° to 106° F. or even higher. In mild cases the skin is moist; in severe ones dry and hot; constipation is usually present; the tongue is clean or lightly coated and its tip and edges red;

photophobia may be pronounced or absent; the pains may be agonizingly severe or very mild in character; nausea may be absent, but usually it is present and followed by vomiting of a clear colorless or yellowish or greenish fluid. The symptoms are all more or less pronounced, depending upon the character of the attack. There may be great epigastric distress and the amount of urine passed may be small, but no albumin is found. At this stage the case resembles one of acute malaria, typhoid fever, or any severe infection. On the second day the temperature may remain elevated or a fall may be observed; the headache and body pains may have abated or they may continue; the photophobia is more marked; the flushing of the face and ocular injection are pronounced; a slight yellowish tinge of the eyeballs can be distinguished. The stomach may be quiet, or the nausea and vomiting may be distressing but somewhat abated. There may be suppression or retention of urine. The skin of the chest is of a dusky hue, and upon pressure it is seen that the capillary circulation is sluggish. On the third day the temperature may remain about the same or fall several degrees and then rise to near its original height, or it may fall gradually and decline during several days by lysis. A sudden drop in temperature to subnormal, with the appearance of black vomit and suppression of urine at this time, almost certainly means a fatal issue. More frequently, after a brief decline on the second day, the temperature rises gradually to 103° or 104° F. and remains there with a morning fall of one or two degrees for one, two, or three days, and then declines gradually to normal. Vomiting may return and the material ejected may contain fly-wing specks or coffee-ground granules, or it may consist of the brownish or brownish-black fluid known as black vomit. The jaundice is now (fifth or sixth day) quite intense, great weakness and prostration are manifested; there may be cramping pains in the abdomen, with the passage of a large amount of tarry material; these may be accompanied or followed by persistent hiccough, delirium, convulsions, coma, and death. The remission or intermission in temperature may occur after twenty-four, forty-eight, or seventy-two hours.

Faget's Sign.—Following the remission or intermission, a singular and progressive diminution occurs in the pulse rate, so that with the secondary exacerbation of fever there is the anomaly of an ascending temperature with a slowing pulse, and this continues regardless of the temperature. With the appearance of jaundice, at this time, the pulse rate diminishes to 70, 60 or even 50 per minute. In well-marked cases this is a valuable and fairly constant sign, but in the milder cases the lack of correlation between pulse and temperature is less apparent.

Epistaxis may be present early, but a more reliable sign is the condition of the gums. At the beginning of the fever they may be swollen and spongy; a day or two later a red line is seen at the margins and upon gentle pressure blood can be made to exude. In severe cases the oozing may be constant and sufficient to stain the lips and tongue. As the disease progresses the tongue becomes, at first lightly, then heavily, coated, and later it may become fissured and bleeding so that the saliva, lips, and tongue, are all blood-stained. Hemorrhages from the mucous

membrane of the mouth, nose, intestine, and genito-urinary tract (especially in females) are frequent after the fifth or sixth day.

Skin.—The skin of the face and chest may bear a blotchy or clean petechial eruption in mild as well as in severe cases, and the appearance may resemble that of a mild eruptive fever. Small macules, papules, pustules, or blebs, may appear after the disease has developed. If these become hemorrhagic the outlook is serious.

Urine.—A trace of albumin is found on the second or third day, and the amount may increase rapidly until the specimen coagulates upon being heated. The albumin usually disappears from the urine with defervescence, but albumin or casts may persist for several months after severe attacks. After a day or two hyaline and finely granular casts appear, and on the fifth or sixth days there are coarsely granular and epithelial casts, which show a more or less deep staining with bile pigment. Red blood cells may be present at about this time and may be scarce or abundant according to the tendency to hemorrhage. The intensely dark color of the urine, about the sixth or seventh day, is due to the presence of bile, though it is not rare to find blood present.

Mortality.—Under favorable conditions the mortality rate should not exceed 10 or 15 per cent.; it should never exceed 20 or 25 per cent. under any circumstances, and a higher death rate would warrant the suspicion that the milder cases were escaping recognition. Now that the diagnosis of "bilious remittent fever" can be excluded, the fact is becoming more apparent that a fairly large proportion of cases of yellow fever are mild in character and recover without black vomit.

Sequelæ.—But few sequelæ follow yellow fever. Recovery takes place quickly, as a rule, and the patient rapidly regains weight and strength. In a small number recovery is followed by a period of weakness and debility which may persist for one or two months. Suppurative inflammation of the parotid and other glands, abscesses, and furuncles, are the only sequelæ that deserve mention, and these yield slowly to the ordinary measures as the patient's strength and vitality improve.

Diagnosis.—The period of incubation being from two to six days, usually from three to five, will aid in determining the probability of exposure in persons who present suspicious symptoms in places removed from the habitat of the disease. The early suffusion of the face and eyeballs, vertigo, frontal headache, pain in the lumbar region and loins, pains in the extremities (chiefly the lower ones, but not involving the joints), nausea and vomiting, with ocular jaundice on the second day, should excite strong and suspicion; and with the accompanying tenderness elicited by deep and gentle pressure in the epigastrium the diagnosis would be reasonably certain. The chill or rigor may be absent, the headache may be occipital, vomiting may not occur, and the temperature may not rise above 102° F. in a mild case. Malaria and most inflammatory conditions can be excluded by examination of the blood. In relapsing fever spirochetes will be present in the blood during the febrile exacerbation; in typhoid fever the bacilli may be obtained in blood cultures; and in these infections albumin is not as likely to be present in the urine on the second day as in yellow fever. Mild cases may be

extremely difficult of diagnosis, but the knowledge of exposure and the symptom-complex, as a whole, with ocular jaundice on the second day, together with marked epigastric tenderness, would justify a provisional diagnosis of yellow fever in the absence of special contraindications. Faget's sign, albuminuria, bloody oozing from the gums on pressure, and fly-wing material in the vomitus, would render the diagnosis complete. In the severer cases the diagnosis becomes clear by the third day at the latest.

A sudden fall in the temperature to subnormal in the first few days, suppression of urine, hiccough, black vomit, and free intestinal hemorrhages, are all indicative of grave attacks.

Guiteras has called attention to some aids in diagnosis. He believes that Ehrlich's diazo reaction is practically never present in uncomplicated cases of yellow fever, although it may be present in severe cases of dengue. He has been able successfully to exclude yellow fever by obtaining the Ehrlich diazo reaction in the urine.

A point of importance in the differential diagnosis between dengue and yellow fever brought out by Van der Berg,[1] is that in dengue there is a leukopenia, the leukocytes being reduced on the average about one-half. Stitt[2] confirms the statement in regard to dengue, in which he finds a polymorphonuclear as well as a general leukopenia, with a marked relative increase of the mononuclear leukocytes. This is in marked contrast to the condition of the blood in the early stage of yellow fever, in which the total leukocyte count is practically normal and there is no diminution in the proportion of polymorphonuclear leukocytes; on the contrary they are frequently increased.

Prognosis.—In every case, no matter how mild, this must be guarded. Even in those which are apparetly trivial, grave symptoms may develop after errors in diet, permitting the patient to leave his bed, or failure to maintain the eliminative functions. A quiet stomach, low temperature, soft skin, the ability to sleep, and a free flow of urine, are all favorable. High temperature without remission, intense and persistent headache, nausea, and nervous irritability, indicate a more serious condition; a temperature above 105° F., delirium, singultus, black vomit, partial suppression of urine, convulsions, dark petechial spots, and hemorrhages into the skin or intestine, are of grave significance. Complete anuria, free intestinal hemorrhages, profuse black vomiting, with hiccough and coma, are of fatal import.

Treatment.—Hygienic and Prophylactic.—The most important duty of the physician during an epidemic, or in the possibility of an epidemic of yellow fever, is to institute preventive measures tending to guard against extension through the agency of the mosquito, and it is necessary to see that proper precautions are taken by non-immunes to exclude the chances of being bitten by mosquitoes that are possibly infected. *Stegomyia fasciata* is a twilight mosquito that feeds, as a rule, early in the morning and in the afternoon until ten o'clock at night. It usually rests in the middle of the day and non-immunes may visit well-lighted

[1] Mense's *Handbuch der tropenkrankheiten*, Leipzig, 1905; vol. ii, p. 98.
[2] *Philippine Journal of Science*, 1906, vol. i, No. 5.

places in infected localities between 9 A.M. and 3 P.M. with almost absolute impunity. But at 3 P.M. the danger begins, and after this hour one should go to high localities without the infected city, or retire within a building thoroughly protected by wire screens. Every measure should be used to reduce the number of mosquitoes. All persons in an infected locality suffering from fever of unknown origin, particularly if it begins with a chill and headache, should be isolated at once and placed behind mosquito-proof wire screens and mosquito netting. These precautions should be continued until the temperature remains normal. As soon as a patient suffering with yellow fever is removed from a room, it should be tightly sealed by pasting paper over all cracks and openings and then fumigated with pyrethrum, using at least one-fourth pound to each one thousand cubic feet. After five or six hours the stupefied insects should be swept up from the floor and burned. Tobacco and sulphur are more efficient but more disagreeable than pyrethrum.

Although there is a general infection with involvement of the blood in yellow fever, disinfection of the person, effects and surroundings of a patient is useless. A quarantine period of at least five days is necessary, and measures should be taken to protect ships against mosquitoes when lying at infected ports. One-fourth of a mile is a safe distance from shore, and the proximity of other vessels should be avoided.

As a matter of personal prophylaxis non-immunes should never spend the night in an infected locality. Should exposure after dark in such localities be unavoidable, then mosquito headnets, heavy gauntlets, and leggings should be worn, and upon retiring the person should see that mosquitoes are expelled from the room or destroyed by fumigation. The sleeping-room selected must be as high as possible above the ground; the bed and its vicinity must be free from mosquitoes and perfectly protected by intact netting of 1.0 or 1.5 mm. mesh. It is unsafe to rely upon the local use of the essential oils, more or less diluted, spirit of camphor, etc., upon the skin.

In the matter of general prophylaxis it is necessary to bear in mind that three factors are indispensible for the production of an outbreak, *viz*: (*a*) preëxisting cases of the disease; (*b*) mosquitoes of the genus *stegomyia;* and (*c*) the presence of non-immunes. These are brought into play in the order stated, and in the absence of any one an epidemic is impossible. The most rational and effective mode of procedure, therefore, is to prevent the interaction of *a* with *b;* if this be effected, *c* may be disregarded. Failing to prevent the contact of *a* with *b*, then if *b* and *c* be permitted to come together after the proper interval, infection results, and can be brought about in no other way, without experimental inoculation.

An interval of about two or three weeks *must* elapse after the importation of the first case before the appearance of secondary cases, and whenever the course of an outbreak is being traced in other than an epidemic locality, it can be safely taken for granted that whenever a group of cases is found to occur together the primary case from which the group originated must have existed two or more weeks earlier. If instead of a group only a single secondary case is produced, the difficulty

will be very great, because it may be assumed that this is the primary case. Two weeks, represents the shortest known developmental or incubative period (twelve days) in the mosquito, plus a short period of incubation in the human being.

Medical.—This is in a sense prophylactic, because by putting the patient to bed early and instituting proper treatment we can lessen the severity of the attack, and in some cases avert a fatal issue.

It is of vital importance that the patient be put to bed and kept perfectly quiet upon the manifestation of the earliest symptoms. The bowels should be moved by a mild cathartic. Usually sulphate of soda is the best, in doses of 4.0 grams (1 dram) every hour, until the desired result be obtained, or six doses have been given. If the bowel fail to respond within an hour after the sixth dose, an enema of soap and water should be given. The saline may be preceded by a small dose of calomel with bicarbonate of soda, 0.23 gram (3 grains) of each, or several minute doses of calomel at short intervals, if the stomach is irritable. Following the catharsis a hot mustard foot bath should be administered, and the patient then be covered with blankets to induce free perspiration. Hot lemonade may be given to aid diaphoresis. If the irritability of the stomach is not relieved a sinapism should be applied locally, and iced carbonated Vichy water in small quantities, or small doses of sodium bicarbonate, 0.2 gram (3 gr.), in cold mineral water, administered. All food must be withheld during the first three or four days, and the patient should be encouraged to drink carbonated Vichy water freely and often, and always ice cold. If this is not at hand any of the alkaline mineral waters may be substituted, after adding about 2.0 grams (30 gr.) of sodium bicarbonate to the pint. The effervescing mixture of Anderson serves an excellent purpose if mineral water cannot be obtained. He adds 30 grains of potassium bicarbonate to a dessertspoonful of freshly expressed and strained lime juice and gives it every two hours while effervescing. He is particular to state that it must be neither alkaline nor acid but neutral. Both Touatre and Anderson state that since their adoption of the Vichy water and effervescing mixture, respectively, they have ceased to see the profuse black vomit and hemorrhages they had formerly observed. For the cephalalgia ice-cold applications are best; the pain passes off after a few hours—twenty-four at most. The coal-tar prepartions and morphine should be avoided as a rule.

In the mildest cases the temperature may remain at about 100° or 101° F. for several days, reaching 102° once and then gradually declining to normal. In a severe case the temperature may ascend to 105° F. or higher at the outset and again in the secondary exacerbation. Such cases require cold sponging every hour or oftener; or the wet pack or cold bath may be used. The former should always be tried first, and in the beginning, if the skin be dry and pungent, sweet spirit of nitre, in doses of 2.0 to 4.0 cc. ($\frac{1}{2}$ to 1 dram) in a little iced water every half or every hour until the skin becomes moist, may be given. The patient should be encouraged to drink alkaline waters freely, and if there be persistent nausea or irritability of the stomach, alkaline fluids should be given cold by rectal injection.

Food being withheld for the first three or four days, the patient should be supplied freely with the fluids already mentioned for the double purpose of allaying thirst and maintaining the renal secretion. It is now thoroughly established that sodium bicarbonate exerts a markedly beneficial effect; whether it is because it remedies a deficiency of alkali or neutralizes an acid poison remains to be shown. After the third or fourth day, if the temperature continues below 101° F. and the patient craves food, he may be given a tablespoonful each of milk and lime-water, cold toast-water, or barley-water, in small quantities and at rather long intervals at first, until the effect has been noted. Pure frozen cream, and gelatine in the form of wine or lemon jelly, are beneficial, and may be given in small quantities if they are enjoyed. After three days of normal temperature, if the patient's condition be good, he may be given milk, chicken broth, blanc mange, ice-cream, or custard, and fresh juicy fruits, followed by soft-boiled eggs, toast, etc.

Yellow fever is characterized by such marked depression with impairment of the circulation that stimulation is directly indicated. No other form of stimulant seems to equal a good dry champagne. It tends to allay nausea and vomiting, is mildly diuretic, and agreeably stimulating. It should be given in small doses of about 15 cc. (a tablespoonful) with ice, every two, three, or four hours, as indicated by the condition of the patient and its effect. It should be given on the second and third days of the fever only when the patient expresses a desire for it, and when the effect upon him is beneficial. The stronger alcoholic stimulants are not so desirable, but they may be used cautiously with persons who are accustomed to and prefer them. They should be well diluted.

If at the outset we preserve the integrity of the vascular endothelium, keep the blood moving within the capillaries, and secure elimination of the maximum amount of toxin, then, if the heart, liver, and kidneys were previously sound, we prevent the occurrence of excessive hemorrhages, and the patient's recovery is practically assured.

It is necessary to observe and record the amount of urine. Retention and suppression are frequent, the latter occurring late and the former early. Every specimen passed should be measured and tested for the presence of albumin, because its early appearance in large quantity may be regarded as an indication of a severe attack. However large the quantity of albumin the physician may feel encouraged if the patient pass from 500 to 1000 cc. of urine in twenty-four hours. Free elimination of the toxin early in the attack lessens the tendency to hemorrhage and modifies the subsequent course. Hence the great importance of instituting eliminative treatment at the earliest moment, and as all toxins are removed chiefly by the kidneys, it is essential to secure early and free secretion by these organs. If black vomit or intestinal hemorrhages occur oil of turpentine in 0.6 cc. (10 minim) doses deserves a trial, with applications of ice to the epigastrium, and alkaline waters and stimulants by the mouth or rectum.

The patient should not be permitted to sit up or leave his bed until after several days of normal temperature.

CHAPTER XXIX

DENGUE

By THOMAS D. COLEMAN, A.M., M.D.

Synonyms.—Dandy Fever, Break-bone Fever, Stiff-necked or Giraffe Fever, Scarlatina Rheumatica, Bouquet Fever (corrupted into Bucket Fever), Polka Fever, Knockel Koorts, etc.

Definition.—Dengue fever is an acute infectious disease with two febrile paroxysms, sharp in onset, short in duration, characterized by intense headache, muscular and joint pains, irregular eruption, and terminating usually in recovery.

Etiology.—Predisposing Causes.—1. *Climate.*—Residence in a tropical or subtropical country, and particularly on the coasts and lines of travel, undoubtedly increases the liability to infection. The ordinary limit of diffusion is generally placed at from 32° 47′ N. to 23° 23′ S. While this is the rule, it has occurred outside of this zone, *e. g.*, in Philadelphia, New York, and Boston. Outbreaks in these sections, occurring in the heated season, confirm the observation that warmth not only favors but is essential to its development.

2. *Season.*—It is strictly a disease of warm weather and disappears with the advent of winter; but in tropical climates it may occur during any month of the year. When it occurs outside of the regions mentioned it appears only during the heated season.

3. *Meteorological.*—Epidemics have occurred in both dry and moist conditions of the atmosphere; but, while a humid atmosphere is not essential, epidemics having occurred in both dry and wet seasons, it undoubtedly favors the spread of the disease. Altitude exercises an inhibiting influence.

4. *Race, sex, age, and social condition* have no influence. Filth, crowding, and unhygienic surroundings appear to favor its development.

Exciting Causes.—It is probable that Graham, of Beirut, Syria, has discovered the chief, if not the only, mode of infection. The history of the disease, its clinical features, and analogy, would lead us to believe it to be produced by a specific organism; and Graham has published observations, which, if confirmed, will fix our knowledge of the etiology. He describes a hematozoan in the blood which differs from that of malaria in its life-history, in that it never forms pigment. He thinks it resembles more closely the *Pirosoma bigemium* (*Boöphilus bovis*) than any other organism. He has never seen it in pairs nor received any suggestion that it multiples by binary division. It possesses the power of amœboid movement, and is to be found both in the body of the red blood corpuscle, from which it often projects motile pseudopodia, and also in the

leukocytes, and floating free in the plasma. Furthermore, it multiplies by sporulation. He found this same organism in the blood and stomachs of the *Culex fatigans* up to the fifth day after they had fed upon the blood of a patient with dengue; and he supports his belief that the disease is transmitted by the mosquito by the following experiments: He placed patients suffering with dengue in apartments which had been freed from mosquitoes and screened, and allowed healthy individuals to remain in close contact with those sick of the disease, and none so subjected developed dengue. He then took mosquitoes which were known to have bitten patients suffering with dengue, and carried them to a small village at a high altitude where dengue was unknown. Two healthy mountaineers allowed themselves to be bitten by the infected mosquitoes. Both developed dengue. The mosquitoes were all killed, and the subjects of the disease kept under mosquito bars until the symptoms of the disease had disappeared, with the result that no other cases developed. Graham also inoculated a human subject with a solution made from the glands of the infected mosquitoes; the patient had a chill on the third day and went through a typical attack of dengue.

Nagib, of Beirut, Syria, confirms Graham's observations in the following experiments, but further confirmations would seem desirable:

1. Fresh specimens examined carefully with the darkfield illuminator showed, in many erythrocytes, small brilliant, light-reflecting bodies, which changed their shape, at one time appearing round and at another fusiform, and moved freely in the blood corpuscles.

2. In specmens stained according to Giemsa-Romanowsky, I was able to find in the erythrocytes small, usually round, but sometimes elongated, fine granulated, from purple to blue-colored bodies of the size of $\frac{1}{5}$ to $\frac{1}{3}$ of a normal erythrocyte, occupying the margin, but also at times the centre of the blood corpuscles. In some specimens these bodies seemed to be half-way outside the corpuscles and in others to have completly left the erythrocytes, the latter, however, are sometimes difficult to differentiate from the blood platelets.

Manson calls the motile parasite a plasmœba, and says it appeared to bore through the border of the corpuscle. The parasite was sometimes irregular, without pigment granules, gradually spreading and growing, often throwing out pseudopodia until it completely filled the corpuscle, the pseudopodia reaching beyond the border of the corpuscles and giving them a crenated appearance. It was actively motile. In a few hours spores would form in the body, the podia of the growth numbering six to ten. These would mature in a few hours, segment, burst out of the cell wall, and float freely in the plasma. The organism is much more active and smaller than the malarial parasite.

The studies of Ashburn and Craig in the Philippines lead them to the following conclusions:

1. No organism, either bacterium or protozoön, can be demonstrated in either fresh or stained specimens of dengue blood with the microscope.

2. The red blood count is normal.

3. No characteristic morphological changes in the red or white corpuscles occur in this disease.

4. Dengue is characterized by a well-marked leukopenia, the polymorphonuclear leukocytes being decreased, as a rule, while there is a marked increase in the small lymphocytes.

5. The intravenous inoculation of unfiltered dengue blood into healthy men is followed by a typical attack.

6. The intravenous inoculation of filtered dengue blood into healthy men is followed by a typical attack of the disease.

7. The cause of the disease is, therefore, probably ultramicroscopic.

8. Dengue can be transmitted by the mosquito, *Culex fatigans Wied*, and this is probably the most common method.

9. No organism of etiological significance occurred in bouillon or citrated blood cultures.

10. The period of incubation in experimental dengue averages three days and fourteen hours.

11. Certain individuals are absolutely immune to dengue.

12. Dengue is infectious in the same manner as yellow fever and malaria.

Immunity.—Our present knowledge does not justify the position that any race or generation of people is immune. Recorded epidemics show that the people of a city are atttacked rapidly, in large numbers, and without regard to race, sex, age or caste. One attack usually protects against another, but two and even three attacks have been observed in the same individual. Dickinson records in the epidemic in Charleston in 1850, that only those escaped the disease who had suffered from it in 1828. A few writers on dengue hold that one attack affords no protection against a second. In this the writer does not concur.

Pathological Anatomy.—In the epidemic at Galveston, Texas, in 1885, Paine observed a "localization of inflammation upon the serous membranes," especially the pleura and peritoneum. Hirsch mentions serous infiltrations in the vicinity of the joints, and reddening of the crucial ligaments of the knee-joints.

Symptoms.—Dengue is a disease of three stages, viz.: (1) invasion lasting from two to five days; (2) remission, lasting from twelve hours to three days; and (3) a return of the symptoms of invasion, lasting from twenty-four to thirty-six hours, in which none of the symptoms are as severe as during the first paroxysm. It has an incubation period of from two to five days, during which time no symptoms may appear, or the patient may experience a sensation of lassitude and anorexia. The onset is sudden; some are attacked while at work or awakened from sleep by the pains. The onset varies with the severity of the attack, in some amounting to trivial discomfort and a few nervous symptoms; in others the invasion is sharp with severe physical and nervous manifestations. Prostration is intense, and is a prominent symptom. In children the disease may be ushered in by convulsions, followed by more or less delirium. Even in adults delirium occurs. In a typical case in adults there are few if any premonitions, the disease being ushered in by a feeling of chilliness, less frequently by a distinct chill. The patient experiences severe pains in the muscles and joints, sufficient to cause him to assume a more or less rigid attitude. The pains in the head,

muscles, and joints, are severe, and in some instances excruciating, making one feel as if the very bones were broken. It is doubtless true, as noted by West, that the most lurid accounts of the suffering come from physicians who have had the disease. The pains seem to affect every portion of the body, but are focalized in the head, back, legs, and joints; they prevent rest, without an anodyne. The knee is the joint most frequently affected, but in some practically all are involved. The peculiar features of these joint manifestations are that while the pain may be intense, there is commonly an absence of swelling; and pain is not produced by pressure on the involved joint. Passive motion of the joint may be undergone without pain, but an effort of the patient to move it is attended by intense suffering. In other cases there is swelling of the involved joints, and pain is produced by pressure and even by passive motion.

There is a rise of temperature which is continuous until the end of the second, third, fourth, or fifth day, when it reaches its maximum. The temperature continues at this height until the third to fifth day, usually the fourth; is followed by sweating and great prostration, when it suffers a remission, and in some cases an intermission, of twelve to thirty-six hours, after which there is a second elevation, which never reaches the former height. In some patients the second elevation of temperature and other symptoms are absent. The temperature varies from 100° to 106° F.; in cases of average severity not going above 103° or 104°; but in severe cases a maximum of 105°, or even 106°, is not infrequently found. The *pulse* is usually bounding, ranging from 90 to 140, and increases in frequency with the fever.

Anorexia is nearly always present, and in some cases marked nausea and vomiting. This last feature is prominent in some epidemics, and since dengue often occurs in close conjunction with yellow fever, has led to difficulty in diagnosis. This is more difficult when more or less jaundice and a heavily coated tongue are present. *The tongue* is usually moist, but covered with a whitish coat; in some cases it may be brown. The countenance wears an anxious look, and is congested from the attendant erythema, giving it a peculiarly bloated appearance. The conjunctivæ are suffused.

The Eruptions.—There are two skin manifestations, the first a vasomotor erythema coming on with the first accession of fever, and the second, the true eruption, which occurs at the second accession of fever, whether this follows remission or intermission. The initial eruption varies in intensity from a simple redness to a distinct erythema. It occurs first on the face, causing it to swell; the conjunctivæ are suffused, and there is tumefaction of the eyelids. Sometimes this extends to the nasal and pharyngeal mucous membranes. It may also extend over the body. Its duration is short. The secondary rash, occurring usually on the fourth to the sixth day, is considered by many as one of the most characteristic symptoms. While this is true in a majority of cases, Bassett-Smith, West, and others note its absence in many cases. Horlbeck states that in the epidemic in Charleston in 1895 the eruption occurred in 40 per cent. of all cases. Certainly the terminal eruption

is present in a majority if not all cases. It appears first on the palms and back of the hands, and extends up the arms; it is also found on the trunk, thighs, and legs. Generally it at first appears as a small elevated circular spot, dusky red in color, disappearing on pressure, and tending to coalesce with contiguous spots, making irregular patches some 2 or 3 inches in diameter. Between these areas the skin looks normal. In some instances, however, the entire integument may be covered by a continuous red blush, giving the patient a scarlatiniform appearance. It leaves in the order in which it appeared. It is characteristic in being not characteristic, some authorities describing it as urticaria-like, some as macular, some as measly, some as roseolar, rubeoloid, etc. These differences may be accounted for in large measure by the variations of the disease. The terminal eruption generally persists for twenty-four hours, but may last longer. When fully developed it is frequently accompanied by some itching and burning.

Desquamation follows the eruption, but is bran-like in character, and never appears in large flakes. It may continue for two or three weeks but is usually over in shorter time.

The bowels are at first constipated, but diarrhœa frequently supervenes toward the later stages. *The urine* is usually high-colored, but is never suppressed and rarely albuminous. Enlargement of the lymphatic glands not infrequently occurs when the fever begins to remit.

Complications and Sequelæ.—Among these may be mentioned: (1) hemorrhages from mucous surfaces; (2) inflammations of serous membranes; (3) delayed convalescence; (4) relapses. Hemorrhages from mucous surfaces, while in some epidemics sufficient to constitute a symptom, are absent in the majority and may be regarded as a complication. These occur from the nose, stomach, intestines, and uterus. In rare instances, pleurisy, orchitis, pericarditis, endocarditis, and meningitis have occurred. Abortion or miscarriage may occur. Convalescence is often slow, extending over weeks and months, and soreness of the muscles and joints may persist or recur at intervals for a long time. Relapses occur a second and even a third time, but usually one attack protects against another.

Diagnosis.—The only diseases with which it is apt to be confounded are yellow fever, influenza, malarial fever, rheumatic fever, and scarlet fever. Yellow fever is a disease of shorter duration. In dengue the pulse is *accelerated* in proportion to the temperature. In yellow fever the pulse is not quickened with the temperature, but slowed. In yellow fever, an eruption is usually not present, and black vomit and jaundice occur, while they are generally absent in dengue. The muscular and joint pains of dengue are not present in yellow fever. The mortality of yellow fever is 30 per cent., while it is almost *nil* in dengue.

Influenza most frequently prevails during cold seasons when dengue could not develop. Influenza is a disease of one febrile paroxysm, and one attack does not protect against another. The nervous and gastro-intestinal types of influenza may stimulate dengue; but the nature of the attack, character of the epidemic, time of year, and finally the presence of influenza bacilli make diagnosis possible.

Malarial fever does not occur in such epidemic form. The febrile disturbance differs from that of dengue, and is relieved by quinine, whereas this drug has no effect on dengue. Finally, the presence of the plasmodium malariæ in the blood would make the diagnosis positive. Dengue should not be confounded with rheumatic fever for the reason that this latter disease does not occur in epidemics. Again, the mortality and complications of the latter disease are far more serious. Pressure on inflamed joints in rheumatic fever causes acute pain, whereas in dengue it usually does not. It would seem to resemble scarlet fever only in the rash and fever; but this is largely a disease of childhood, while dengue attacks all ages, and occurs in all seasons while dengue occurs only in warm weather. Scarlet fever is accompanied by the characteristic "strawberry tongue" and ulcerated fauces, is a disease of one febrile paroxysm, is not attended by muscular and joint pains, and is followed by extensive desquamation.

Prognosis.—Except in those already affected with other disorders the mortality is almost *nil*.

Treatment.—Prophylaxis.—So long as a susceptible individual is in the epidemic area, absolute protection is almost impossible. If the *Culex fatigans* is responsible for the transmission much would be gained by warfare against this insect.

Diet.—The diet should be liquid; when marked anorexia is present, often the only nourishment retained is egg albumen. The diet should receive special attention throughout for no such benign disease produces such marked prostration and has frequently such a tardy convalescence.

External Applications.—Hot baths reduce the temperature and reduce the nervous symptoms. When these fail to reduce the temperature, or cannot be given from the pain attendant on movement, cold applications may be made to the head, and the body sponged. Much comfort may be given by rubbing the back and joints with a liniment of equal parts of oil of wintergreen and spirit of camphor.

Medical Treatment.—The bowels should be well moved, preferably with broken doses of calomel followed by a saline. The three most urgent symptoms are pain, fever, and insomnia. In cases of moderate severity a pill consisting of salicin, gr. v (0.33 gm.), and Dover's powder, gr. j to ij (0.13 gm.), will suffice, being repeated every four to six hours as indications warrant. The coal-tar derivatives are especially valuable and phenacetine or antipyrine with codeine and citrate of caffeine may be given. The following pill three or four times a day will be found efficacious in a majority of cases: phenacetine, gr. v (0.33 gm.), codeine, gr. $\frac{1}{4}$ to $\frac{1}{2}$ (0.015 gm.), camphor monobromate, gr. j (0.065 gm.).

When the joint symptoms are severe the salicylates, alone or in combination with an opiate, will be found effective. In a certain number these will not avail, and morphine will be indicated either by mouth or rectum, but a hypodermic of gr. $\frac{1}{4}$ (0.015 gm.) will be found most efficient. This must be repeated as necessary. Quinine may be given for its antipyretic effect, but so far as known it has no value as a prophylactic and does not cut short the disease. Some authorities consider it not only valueless but harmful.

CHAPTER XXX

RABIES

By MAZŸCK P. RAVENEL, M.D

Synonyms.—English, Hydrophobia, Madness; French, La rage, L'hydrophobie; German, Hundswuth, Tollwuth, Wuthkrankheit, Wasserscheu; Italian, Idrofobia, Rabbia, Lyssa.

Definition.—Rabies is an acute, specific, rapidly fatal malady, communicated to man from some lower animal. It is always an inoculation disease, that is, communicated directly through a wound usually made by the teeth, the infective matter being the saliva, which contains the virus, the exact nature of which is unknown.

Distribution.—Rabies occurs in almost every part of the world, Australia being the only country known to be exempt, owing to the rigidly enforced quarantine. It is very rarely seen in Holland, Denmark, Norway, Sweden, and Switzerland. In France, Belgium, Hungary, and Russia the disease is widespread. In the latter country it is common among wolves. It is quite common in Italy and Spain, although the official figures are small. In Germany the disease is seen mainly on the frontiers and is rare in the interior. It is quite common in China and Japan. Britain is practically free at the present time. Canada has been severely visited in late years. Rabies occurs in practically every part of the United States. Until 1909, the disease had not been reported west of the Rocky Mountains, but severe outbreaks have recently taken place at widely separated points on the Pacific slope. In 1908 there were 534 known infected localities in the United States, in 1911 there were 1381. The census for 1900 gave 123 deaths. Salmon collected statistics from the health officers of 73 cities which showed 230 deaths between 1890 and 1900.

Animals Affected.—All mammalia are susceptible, and birds also contract rabies when bitten or otherwise inoculated. Dogs are most frequently affected, and to them we owe the perpetuation of the disease. It is not infrequent among wolves, foxes, hyenas, jackals, skunks, etc. Cats are rarely affected. Among the domestic animals cattle are most often affected, swine least so. It is uncommon in horses. In England it has appeared among the deer in parks. The money losses from rabies are very heavy.

Etiology.—Hydrophobia being always the result of accidental infection from some lower animal, its incidence will follow closely that of rabies in the domestic animals, especially the dog, which is by far the most frequent source not only for man but for all other animals. Statistics of 16,172 persons bitten by supposedly rabid animals, collected

at the Pasteur Institute, Paris, incriminate dogs in 15,021 cases, cats in 959, wolves in 14, foxes in 2, jackals in 9, horses in 32, asses and mules in 40, cattle 67, sheep 3, pigs in 12, and man in 13. The danger following the bite of a rabid animal depends on the species, and the location and extent of the wounds. The bite of wolves is more apt to be followed by rabies than that of any other animal, owing partly to the greater activity of the virus, and partly to the savage mode of attack, the wounds being very extensive, lacerated, and often located about the head and face. Next in point of danger come bites from cats, then dogs, and lastly other animals. The report of the Pasteur Institute at Kharkoff for the ten years, 1892 to 1901, shows that of 8430 persons bitten by rabid dogs, 77, or 0.91 per cent., died, whereas of 193 bitten by rabid wolves, 32, or 16.58 per cent., succumbed to rabies. The herbivora are apt to cause contusions with their blunt teeth, rather than punctured or lacerated wounds. Farmers are not infrequently exposed to infection from cattle through attempts to drench them, or from putting the hand in the throat in cases of "dumb" rabies, in order to remove a supposed obstruction.

Bites on exposed parts of the body are more dangerous than those made through clothing, since the latter retains the virus, and the comparatively clean tooth enters the body. For the same reason long-haired dogs when bitten escape infection more often than short-haired ones.

Bites in parts of the body having a rich nerve supply, as the face and hands, are particularly dangerous. In the former case especially, the virus is rapidly conveyed to the medulla. The same is true of bites in or about the large nerve trunks of the extremities.

The comparative danger is well shown in the statistics of 18,645 treated at the Pasteur Institute in Paris, as reported by Pottevin.

Location of bite.	Number treated.	Deaths.	Per cent.
Head	1,608	21	1.36
Hands	10,254	49	0.47
Limbs	6,783	20	0.29

Interesting figures on the same point are given from the Pasteur Institute at Kharkoff for the years 1892 to 1901.

Location of bite.	Number treated.	Deaths.	Per cent.
Upper extremities	5301	34	0.64
Lower extremities	2601	2	0.08
Head and face	946	73	7.72
Body	542	0	0.

Rabies may be transmitted by the deposit of saliva containing the virus on abraded surfaces, as by licking. It may also be contracted through wounds received in making autopsies on animals or persons who have succumbed to the disease. In all cases a solution of continuity is necessary for the absorption of the virus; it cannot pass through the healthy skin. It is doubtful if the virus can be absorbed through the digestive tract.

Not every person bitten by a rabid dog becomes infected. Leblanc,

as the result of careful investigation, gives 16.6 per cent. as the proportion, an estimate which is generally accepted as conservative and correct. Some series of cases show much higher figures. Bouley reports 152 deaths among 266 persons bitten, but of these, 120 were bitten on the face and hands, the greater danger from which has been noted.

Sex.—Men are not only more liable to be bitten by rabid animals, owing to their various callings, but when bitten are more apt to contract hydrophobia. This is doubtless due to the greater protection afforded by the skirts, and not to any inherent immunity in women.

Age.—Two-fifths of all cases occur in children under fifteen years of age, according to Bollinger. Children are particularly liable to bites, owing to their habit of collecting together for play in the streets, their inability to recognize danger, and their lack of defence. For obvious reasons they are often bitten about the face. On the other hand, they appear to enjoy considerable relative immunity. Brouardel says that of every 100 persons below twenty years of age bitten, 31 die, while above this age, 62 of every 100 die.

Influence of Season.—The statistics of the Pasteur Institute, Paris, from 1886 to 1893, show that the largest number of patients apply for treatment in March, April, and May; the smallest in September, October, and November.

A table compiled by D. E. Salmon, including 14,066 cases of canine rabies, gives the following results by months: January, 943; February, 1045; March, 960; April, 1323; May, 1419; June, 1467; July, 1435; August, 1294; September, 1145; October, 965; November, 933; December, 1137. It is seen that more cases occur from April to September, inclusive, than during the rest of the year, due, no doubt, to the fact that dogs are more apt to run abroad during the warm season. Season and temperature have no real influence on the prevalence of the disease.

Virus.—Distribution.—The virus is always contained in the saliva, and appears to be excreted chiefly by the parotid gland, though not entirely so. The salivary glands themselves are virulent, though not so constantly as the mixed saliva. The saliva of the dog has been shown by Nocard and Roux to be always virulent twenty-four to forty-eight hours before the animal shows any symptoms of illness. The lachrymal glands, the pancreas and suprarenal capsules may contain the virus. It is also excreted in the milk at times. The blood and lymph are very rarely virulent, and Helman has shown that the virus is absent from the lymph glands in relation to the point of inoculation. The muscles and organs are innocuous.

Every part of the central nervous system constantly contains the virus, but it is especially concentrated in the medulla. The large nerve trunks are usually virulent, as is also the cerebrospinal fluid. Pasteur showed that the "entire nervous system, from centre to periphery, is capable of cultivating the virus." Roux found that the peripheral nerves, even on the side opposite inoculation, were often virulent.

Nature.—The exact nature of the virus is unknown. The behavior of the disease makes us certain that it is caused by a specific micro-

organism, which, after introduction into the body, undergoes a period of incubation, during which it multiplies and produces a toxin having a special action on the central nervous system, as is the case in tetanus, to which it bears a striking analogy. Nocard in 1880, and Paul Bert in 1882, showed that, on filtration through plaster, the virus was held on the filter, the filtrate being devoid of pathogenic power. Further studies have shown that the virus will frequently pass a coarser filter, such as the Berkefeld V, and will sometimes penetrate a Chamberland F, under pressure. Several observers have found that the filtrate frequently produces cachectic and paralytic phenomena not unlike rabies in dogs and rabbits, but after death the medulla of the animal is incapable of injuring other animals, showing that the condition is a toxic one. In this respect also the analogy to tetanus is close, and from this fact the disease has been considered a toxoneurosis. Serial passages through susceptible animals increase the power of the virus, while it is attenuated by drying, heat, light, etc., as many bacteria are.

Innumerable attempts have been made to discover the causative agent, and, from time to time, observers have announced the finding of cocci, bacilli, yeasts, and protozoa, which they believed to be the pathogenic organism. None of these discoveries has stood the test of rigid investigation. At the present time, the belief is growing that the cause of rabies is a parasitic protozoan discovered by Negri and generally known as the "Negri body." This was the opinion of Negri from the first. His discovery has been amply confirmed, and most observers agree with his interpretation of the nature of the bodies as well as their significance. Negri has traced a developmental cycle for the parasite, and classified it with the sporozoa. Williams and Lowden[1] have also worked out a developmental cycle for the organism, placing it in the class protozoa. Williams has named it *Neuroryctes hydrophobiæ*. Calkins does not consider the life history as given by Williams and Lowden as entirely established. He believes, however, that the organism is a protozoan but is not willing to accept the subclassification sporozoa.

A small minority of scientists oppose these views. Babes regards the Negri bodies as specific reaction products, indicating resistance on the part of the cell to the invading parasite, which may be demonstrated by special staining as granules in the interior of the bodies. The Negri bodies are therefore encapsulated parasites undergoing involution or degeneration. By others they are regarded as being cell degenerations or inclusions. The constant presence of the bodies in rabies, and their absence from the brain in other diseases and in health is admitted universally.

Resistance.—The virus is destroyed by heat, drying, and light. In dry air, protected from the light and from putrefaction, the spinal cords of rabbits lose their virulence gradually in fourteen to fifteen days, a fact made use of by Pasteur in preparing his vaccines. When in thin layers, the virus is entirely destroyed by drying in four to five days. Direct sunlight destroys it in about forty hours. In water the virus

[1] *Journal of Infectious Diseases*, 1906, vol. iii.

retains its power for twenty to forty days, or longer. Neutral glycerin preserves it unchanged for a long time. Roux found that after four weeks in glycerin at 30° C. the virus was unchanged in pathogenic power.

Galtier has found the virus active in the central nervous system of rabbits buried for twenty-three days, of sheep buried thirty-one days, and of dogs buried forty-four days. It is not injured by cold, resisting the prolonged application of a temperature 10° C. to 20° C. below zero. It is destroyed by 50° C. in one hour, or 60° C. in a half-hour.

Investigators differ greatly as to the effects of various antiseptics. The best appear to be corrosive sublimate, 1 to 1000, citric acid in 6 per cent. solution, and saturated watery solution of iodine. The virulence of fixed virus is destroyed in eight minutes by 1 part of a 5 per cent. solution of formalin to 3 parts of virus. Mixed in equal parts it is destroyed in five minutes. Bile rapidly destroys the activity of the virus. When an emulsion of the bulb from a rabid animal is mixed with an equal volume of bile from either a healthy or rabid rabbit, and allowed to stand a few minutes, it may then be inoculated without danger of causing rabies.

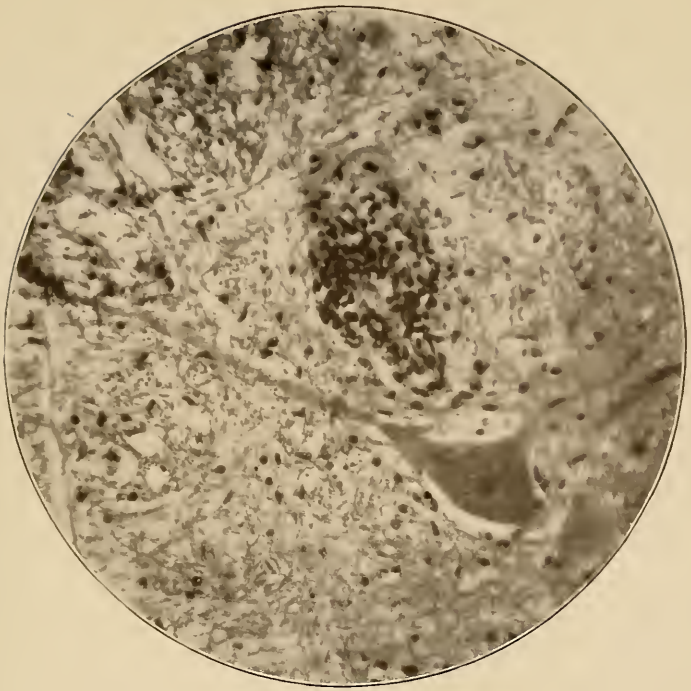
Penetration.—From the point of inoculation the virus makes its way to the central nervous system along the nerve trunks, producing no symptoms until the central system has been the seat of the virus for some time. If the spinal cord of an animal is cut, and a virulent inoculation then made in the hind extremity, it will be found, after a suitable period of incubation, that the spinal cord below the point of section is virulent, while above, it contains no virus. When the inoculation is made into the brain or upper extremity, the descent of the virus can in like manner be prevented by section of the cord. Roux has shown that in rabies developing slowly after inoculation of the limb on one side, the virus may also be found in the peripheral nerves of the opposite side; if, however, the period of incubation is short, only the nerves on the wounded side contain the virus. Clinically it has been observed that the paralytic and convulsive phenomena are more marked on the side of the inoculation. Experimentally in small animals the circulation and lymph channels appear to play some part in the absorption of the virus.

Pathology.—There are no characteristic gross pathological changes. In man, congestion of the lungs and emphysema are common, due to the convulsive seizures. The muscles of the chest and pleuræ are sometimes ruptured in the same way. Congestion of the fauces, œsophagus, stomach, and larynx is commonly found. Of the internal organs, the kidneys, spleen, brain, and spinal cord show congestion.

Pathological Histology.—Many authors have described lesions of the nervous system which have been thought more or less characteristic. Babes has described what he considers the essential lesion of rabies—an accumulation of embryonic cells in the neighborhood of the central canal, and especially about the large modified cells of the motor centres of the bulb and cord. In the bulb he describes the pericellular accumulations of embryonal cells found by Kolessnikoff, for which he proposes the name "rabic tubercle." The cells of the bulbar nuclei undergo degeneration and show the various stages of chromatolysis. There is

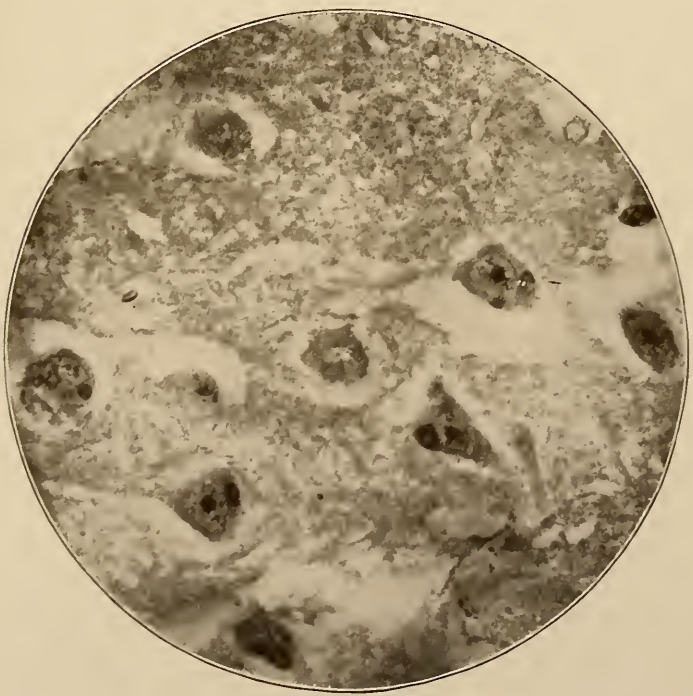
PLATE XXXIII

FIG. 1



Rabic Tubercle from Medulla.

FIG. 2



Negri Bodies in Pyramidal Cells of Hippocampus.

loss of the prolongations and progressive modification with even total disappearance of the nuclei, a dilatation of the pericellular space, and an invasion not only of this space, but also of the nerve cells by embryonal cells; at the same time, there appear small corpuscles which are hyaline, brownish, and in parts metachromatic. Many of the nerve cells become surrounded by a large zone of embryonal cells, degeneration of the cell follows, and when complete the embryonal cells occupy the cell area entirely, forming the "rabic tubercle."

In 1900 Van Gehuchten and Nélis discovered what they believed to be a diagnostic lesion. While recognizing and confirming many of the lesions described by other writers, they consider them secondary and of little importance. They believe that the virus acts by preference on the peripheral cerebrospinal and sympathetic ganglia. The lesions consist of atrophy, invasion, and destruction of the nerve cells by new-formed cells, due to the proliferation of the cells of the endothelial capsule. The new-formed cells increase in number, invade the protoplasm of the nerve cell, and finally occupy the entire capsule, the nerve cell proper having completely disappeared, while in its place is seen a mass of round cells. In advanced cases practically all the nerve cells may be destroyed, and the section has much the appearance of an alveolar sarcoma. These changes have been found in a great variety of animals.

In 1903 Negri announced the discovery of certain bodies in the nerve cells of rabid animals. They are found especially in the horn of Ammon. They are from 1 to 23μ in diameter, oval, round or triangular in shape, according to their size and position in the cell. They are strongly eosinophilic and consist of a fundamental substance, which is homogeneous and hyaline in appearance. Within them are clear areas which appear to be vacuoles, in many of which granules may be found. There is usually a large central body surrounded by smaller ones. Aster-like forms are often seen. These inner bodies vary considerably in size, structure, and staining reaction, but are usually basophilic. The bodies vary greatly in size and number in different cases, and seem to be affected by the species of animal. In cattle they are usually numerous and large. Budding forms are frequently observed. They are especially numerous and large in cases of long incubation period (Negri). They are generally most numerous in the large nerve cells of the horn of Ammon, fewer in the cerebral cortex, the cerebellum, the medulla, and least of all in the spinal ganglia and vagus. They are quite resistant to external agencies, remaining unchanged for some days by putrefaction and one hundred and eighty-three days by desiccation. Material may be preserved in glycerin for eighty days without altering the Negri bodies. They are destroyed by a 33 per cent. solution of caustic potash.

Postmortem Diagnosis.—There are no gross lesions which enable one to state positively that death has been due to rabies. In dogs, perhaps the most constant feature is the absence of food from the stomach and the presence of foreign matter, such as straw, wood, hair, etc. Emaciation is usually marked and putrefaction takes place rapidly.

Until recently we have been obliged to resort to inoculation of animals for a positive diagnosis. Rabbits are usually selected, and the inoculation

made under the dura, since infection is more rapid and certain than when the inoculation is made elsewhere. Symptoms appear from the sixteenth to the twenty-first day, as a rule, but may be delayed for sixty days. The type of rabies following inoculation is usually the paralytic, though rarely the furious type is seen. The virus of rabies is concentrated in the medulla, and especially in the floor of the fourth ventricle. For inoculation the tissue is by preference taken from this area.

Microscopic Diagnosis.—On account of the time required, the inoculation of animals is of no service in determining the necessity of antirabic inoculations. Fortunately it is now possible to make a rapid diagnosis by microscopic methods. For diagnosis by the method of Van Gehuchten and Nélis, the plexiform ganglion of the pneumogastric nerve is selected, as it is easily dissected out, and presents the characteristic changes in the ganglion cells. In dogs, the ganglion is readily found by cutting down on the pneumogastric nerve in the neck, and following it up. Near the skull it divides into two branches, on one of which, the smaller, is found a small, oval, reddish ganglion, the cervical. The larger branch enters the plexiform ganglion, which is easily recognized by its fusiform shape, and white or grayish color. It is seldom more than a half-inch from the foramen, and it is generally necessary to cut the nerve as it emerges from the skull. The ganglion may be prepared for section by any of the rapid methods.

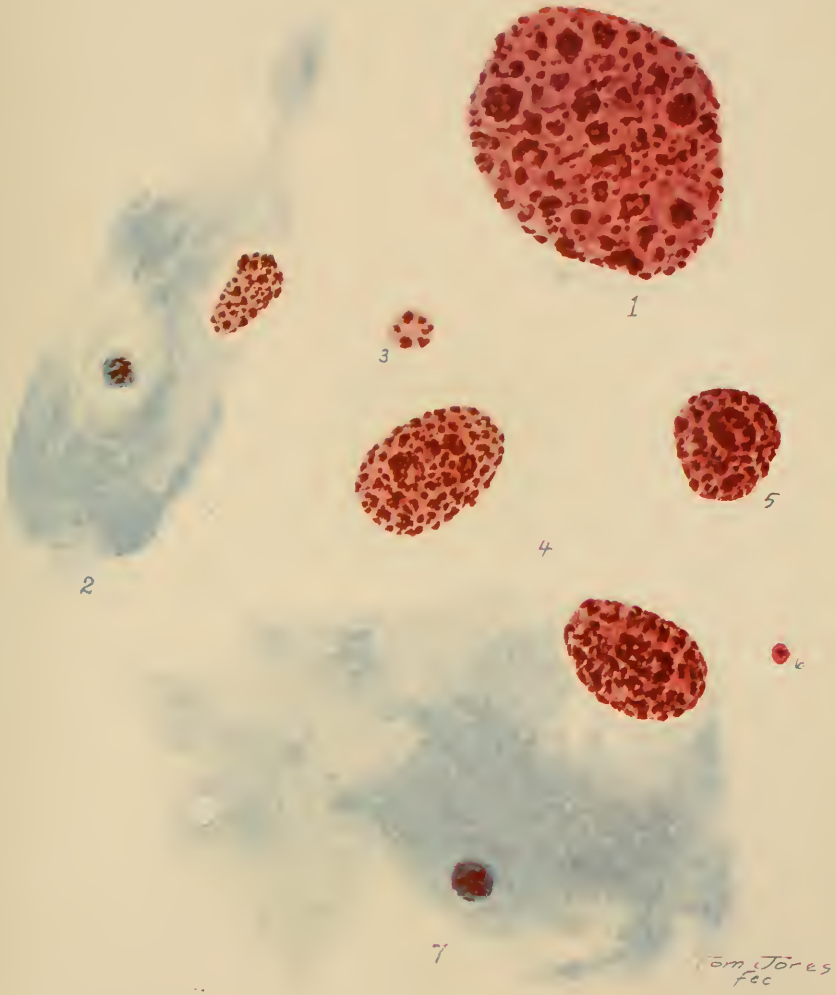
The best stain for general use is hemalum (Grubler), made up with a 0.5 per cent. solution of carbolic acid, and counter-stained with eosin. While the lesions cannot be considered specific, since similar changes have been noted occasionally in other toxic conditions, and in the ganglia of aged dogs, yet by their extent and constant occurrence in rabies they have an unquestionable significance, and, taken in connection with even a meager history, have an absolute diagnostic value. Certain precautions must be observed: The animal must be allowed to die of the disease. The lesions may be slight or entirely wanting in animals killed prematurely, and in such cases their absence does not preclude the existence of rabies. If absent after death from the disease, we can positively deny the existence of rabies.

A diagnosis can be made within twenty-four hours by rapid fixation and mounting, and is easily made within forty-eight hours.

The diagnosis by the *method of Negri* has advantages over the above in that the Negri bodies are usually found early in the disease, are not affected by putrefactive changes incident to delay in obtaining the material, and the technique is more simple. In practice a small portion of the brain should be taken from the cortex of the cerebellum, and also from Ammon's horn, as the bodies may be numerous in one area and not in the other. The pieces of tissue may be fixed in Zenker's fluid, embedded in paraffin, and stained with eosin and methylene blue. The bodies show red against the blue background of the cell. The stains of Mann and Romanowsky are especially recommended.

An immediate diagnosis may generally be made by the smear method of Williams. Minute portions of brain substance are taken from the cerebral cortex about the crucial sulcus, the cortex of the cerebellum,

PLATE XXXIV



Negri Bodies from Horn of Ammon of Dog.

Stained by Harris' method. (Jour. Infect. Dis., 1908, v.)

and the hippocampus major. Crush these between two well-cleaned slides, and make a smear by drawing them apart lengthwise under gentle pressure so as to produce an even and fairly thin film. Dry in the air and fix in methyl alcohol for three to five minutes or in Zenker's fluid for fifteen minutes. Many methods of staining are in use. Among the best are Giemsa's solution, the eosin-methylene blue of Mallory, the rosaniline-methylene blue of Van Gieson, especially as modified by Moon, and the eosin-methylene blue method of Harris.[1] This last gives especially beautiful pictures, and is carried out as follows: (1) Fix smear in methyl alcohol one minute. (2) Wash in water to remove alcohol. (3) Immerse in old saturated solution of eosin in 95 per cent. alcohol one to three minutes (solution must be at least two months old). (4) Wash two or three seconds in water to remove excess of eosin. (5) Immerse in fresh solution Unna's alkaline methylene blue five to fifteen seconds. (6) Wash briefly in water. (7) Decolorize in 95 per cent. alcohol, blot, and dry in air. The entire process requires less than five minutes.

Moon's stain is very simple: To 10 cc. of water add 2 or 3 drops of a saturated solution of rosaniline in acetone (U. S. P.), agitate with a pipette and add 2 drops of a one-half saturated solution of methylene blue in water. The fixed smear is flooded with the mixture, and staining is accomplished in one to two minutes without heat. The bodies appear magenta red, while the granules are deep blue.

The discovery of Negri has been abundantly confirmed in every part of the world. While there is still some doubt as to the exact nature of the bodies, it is certain at least that they bear a close relation to the causative parasite. They are found only in rabies, and their presence enables one to make a positive diagnosis. Bertarelli states that in more than 1000 examinations Negri bodies were never found in animals free from rabies, and on the other hand, were present in all infected animals, with three exceptions. Williams quotes Luzzani as saying that of 457,297 cases of rabies as proved by the biological test only 9 failed to show Negri bodies in sections.

Incubation.—The average period in man is about fifty days, but it varies between wide limits. The great majority of cases occur between the twentieth and ninetieth day. Cases have been reported as developing several years after infection but are generally discredited. Gowers says, "It is, however, certain that the disease may occur after an interval of a year or eighteen months, and it is difficult, therefore, to deny the possibility of a longer interval." The shortest period of incubation is about twelve days. The development of rabies is not common after three months, and is quite rare after six months. The period of incubation is influenced by the location and severity of the injury, and apparently by the species of animal inflicting the bite. It is apt to be shorter when the bite is about the face or neck, or into large nerve trunks. Women show a shorter period than men, and children shorter than adults. Bites by wolves give shorter incubation than dogs, though this may be

[1] *Journal of Infectious Diseases*, 1908, vol. v.

due to the greater severity of the attack and the location of the injury, which is usually about the head.

Symptoms.—As a rule, there are no symptoms during the period of incubation. The wound generally heals as any other similar injury without local thickening or glandular involvement. In some cases mental depression is marked, but it is usually due to anxiety and apprehension rather than to the disease. Instances have, however, been reported by most reliable observers in which mental symptoms were noted in children too young to be apprehensive of danger, and in persons who were not aware that they had been bitten by a rabid dog. Three stages are usually recognized, but are not always well defined. The symptoms of the later stages are frequently prominent from the first.

1. **Premonitory Stage.**—This is often marked by irritation, tingling, or a feeling of numbness at the seat of the bite, or quite severe pain, lancinating in character, and radiating up the limb. These sensations may exist for as much as a week before other symptoms appear, although usually this stage lasts only twenty-four to forty-eight hours. The patient complains of general malaise, depression and melancholy, with extreme anxiety and a sense of impending danger. The sleep is disturbed; often there is great restlessness and irritability.

About this time symptoms referable to the throat appear, such as slight difficulty in swallowing liquids, or a slight choking sensation. The voice becomes husky, often there is precordial distress, with a sense of oppression, the patient frequently taking deep inspirations. Slight fever with increase of pulse-rate is commonly present; occasional rigors occur. During the early stages of the disease many patients show symptoms very much like those characteristic of rabies in the dog: an unnatural suspicion, irritability of temper, surliness, desire to be alone, alternating with periods of mental excitement and loquacity. Delusions and maniacal delirium appear as late symptoms.

2. **Stage of Excitement.**—The symptoms all increase rapidly in severity. The face takes on an expression of terror with marked pallor; the muscles are drawn and restless; the eyes have a "hunted look." There is intense thirst, but every attempt to swallow water brings on a spasm of the muscles of deglutition and respiration—the typical hydrophobic spasm. The extreme thirst impels the patient to make strong efforts to drink. The water is taken into the mouth, but as soon as it touches the fauces, it is expelled with considerable force, and violent spasmodic contractions of the muscles of deglutition and respiration come on. These attacks are accompanied by a sense of extreme dyspnœa, "even when the glottis is widely opened or tracheotomy has been performed." They increase both in intensity and frequency, and there develops a cutaneous hyperesthesia, in consequence of which the slightest draught of air, or contact with anything cold, is sufficient to determine an attack. The suffering of the patient, both physical and mental, is intense during the spasms, and the dread of them produces a mental condition which increases the ease with which they are excited. The hypersensitiveness is so marked in some cases that the sight or sound of water, or even the verbal suggestion of it, a strong light, or the reflection from a polished surface

or looking-glass, is sufficient to bring on a spasm. To this dread of water, acquired by experience of its effect, is due the name "hydrophobia." In man these spasms constitute at once the most distressing feature of the disease, as well as the most diagnostic symptom.

With the advance of the disease, the convulsive attacks, which were at first confined to the muscles of deglutition and respiration, involve other groups of muscles and become general. They may be tetanoid with marked opisthotonos and suspension of respiration, or else be "coördinated and closely resemble hysteroid convulsions." Not only is the frequency and intensity of the seizures increased, but the length of the paroxysms often becomes greater and death from asphyxia may occur. The skin and patellar reflexes are usually increased. Much distress is frequently caused by auditory and olfactory hyperesthesia. Slight odors precipitate attacks of sneezing and even convulsions.

The mucous surfaces are covered with thick tenacious mucus; the saliva is abundant and viscid, while inability to swallow it is often present. There are constant attempts to expel it, which are only partially successful, so that it hangs from the patient's mouth. Vomiting is frequent, the ejected fluid being greenish brown and sometimes containing blood.

The horror of the convulsive attacks is so great that delusions or even maniacal delirium often appear. The delirium is most marked during the paroxysms; the patient may throw himself from the bed, and even inflict severe wounds on himself without apparent pain. He may attempt to bite his attendants or spit at them. During the convulsions noises are made in the throat which have often been described as resembling the bark of a dog. The delirium is not constant. During the intervals the patient can be brought to consciousness. He often shows anxiety for the safety of those about him, begging to be restrained from injuring them. The duration of this stage is from one and a half to three days.

3. **Paralytic Stage.**—The convulsive attacks, with the attendant mental symptoms, usually abate a short time before death, a paralytic condition taking their place, and the patient sinks rapidly, dying from exhaustion. Coma may precede death.

Temperature.—Babes lays stress on an elevation of temperature during the period of incubation. This has often been observed in animals, but its constant occurrence in man remains to be proved. In the early stages, elevation of temperature is lacking or moderate, and throughout the disease may not exceed 100° or 101° F. Usually the temperature rises as the symptoms increase, reaching 103°, 104°, 105° F., or even more, just before death.

The urine frequently contains albumin, sometimes sugar and blood.

The pulse is quick throughout. During the last stages it becomes more rapid, small in volume, and irregular. Increased sexual desire is not infrequent in the early stages and may increase as the disease advances. Persistent priapism may add to the difficulty of urination.

Paralytic Rabies.—Sometimes the convulsive attacks, the excitement and delirium, and the hydrophobic spasms are entirely lacking, and

we have typical paralytic rabies, so often seen in dogs and in animals inoculated experimentally. This type is especially apt to follow extensive bites when the amount of virus is large. According to di Vestea and Zagari, it is apt to follow bites about the lower extremities, while the furious type is usually the result of bites about the head and hands. The first symptoms are usually in the bitten limb, but sometimes violent pains extend from the lower trunk down the limbs, which feel heavy and difficult to move. Paraplegia soon comes on, and may be the first symptom. The course of the disease is an acute ascending paralysis, involving the sphincters and the muscles of the trunk, and ending in death by paralysis of the muscles of respiration, or by cardiac syncope. Diagnosis may be impossible except by inoculation of animals, and microscopic examination after death.

Duration.—Death usually occurs between the second and fifth days; rarely the patient may survive eight or nine days. Bouley found that of 90 cases, 74 died during the first four days—most of them on the second and third days. In 16 cases life was prolonged beyond the fourth day. In the paralytic type death often does not take place until the seventh day.

Rabies of the Dog.—The disease is seen in two types, a furious, and a tranquil or paralytic type.

Furious Type.—In the furious type the first symptoms consist solely in changes in disposition, manifested by distress or uneasiness, and restlessness. The animal is easily excited. At this stage, he does not usually show a disposition to bite; he is still docile and obeys orders, though not so quickly as in health; he soon seeks solitude and shows a disposition to hide in dark corners, or burrow in the straw of his kennel; periods of calmness alternating with marked excitement are observed; he still shows affection for his master but may be irritated by strangers, or, being surprised by touch or blow, may inflict a bite. The appetite is still good and may be excessive. Soon the restlessness becomes more marked; the dog is constantly in motion; he is apt to tear carpets, rugs, etc., which may be in the room with him; he shows signs of delirium, looking off into space apparently seeing some imaginary object; at times he will attack an imaginary enemy. He will still respond to his master's voice, but his attention cannot be held for any length of time. At this early stage, the voice becomes modified, and this may be regarded as one of the most typical symptoms. Instead of the clear and sharp bark which is natural, the latter part of the note becomes prolonged and of a higher pitch, going off into a plaintive cry, which has been likened to that of a dog fatigued in the chase, and in succeeding short barks which may follow, the jaws do not close completely.

While this symptom is a striking one and quite constant, it may be lacking at times and certain dogs remain quiet. The appetite diminishes about this time; food is taken with more or less difficulty, and soon it is refused, swallowing having become painful and difficult. The animal may appear to have a bone stuck in its throat, a symptom which often tempts the owner to make an examination for some obstruction. There is no fear of water, and the animal drinks water and other liquids quite

greedily, until paralysis of the constrictor muscles of the pharynx makes swallowing impossible.

The excitement becomes marked and the animal is now furious. If a stick or other object is presented to him, he seizes it with power, and attacks the bars of his cage. If at liberty, he attacks everything in his way, swallowing all sorts of articles, such as wood, paper, straw, and stones. At this time he begins to wander, running with mouth open; the eyes have a wild look; he attacks every object or animal which comes in his path. As a rule, he runs straight ahead and does not turn out of his way to attack animals. The dog may travel tremendous distances, but is apt to return to his home, exhausted and covered with dust and blood; or else he may continue his course until he falls exhausted, as many as fifty miles being covered. Very soon paralysis sets in, commencing in the hind legs, and finally becomes general. The dog is no longer able to stand; weakness becomes more marked and stupor sets in, which becomes deeper and ends in death. The course of the disease is rapid, covering from six to ten days, and averaging from four to five days. The symptoms are so characteristic that they can scarcely be mistaken for any other disease. The furious type is the most common.

Paralytic Type.—The paralytic type, ordinarily spoken of as "dumb rabies" constitutes from 15 to 20 per cent. of all cases. In certain countries, as in Turkey, it is the prevailing type, which explains the relative rarity of rabies in man in this country where dogs abound. The commencement of the disease is the same as in the furious type, but the accesses of fury are lacking. For several days the dog appears restless, seeking seclusion and dark places. The paralysis may commence in various parts of the body, but, as a rule, affects first the muscles of the jaw, which soon drops, the dog being unable to close its mouth, and the tongue hanging out; the whole expression of the animal is pitiful in the extreme; an abundance of saliva runs from the mouth; the taking of water is impossible; the mouth becomes dry, covered with dust, and brownish in color. The animal is quiet; he does not respond to provocation, nor does he seem to wish to bite. The progress of the disease is more rapid than in the furious type. The paralysis extends, and death occurs on the second or third day.

In the "dumb" type it is common to suspect an obstruction in the throat, and in the attempt to locate it the saliva may infect wounds of the hand. The animal never wanders and, being unable to bite, the danger of transmission is slight.

Diagnosis.—Hydrophobia may be confounded with tetanus, hysteria, acute mania, and lyssophobia.

From tetanus it is distinguished by the longer period of incubation, the absence of trismus and the "risus sardonicus," and the complete absence of spasm during the intervals. The mental condition is different; the anxiety and the restless irritability of hydrophobia are lacking in tetanus. The most characteristic symptom of hydrophobia is the respiratory spasm excited by attempts to swallow water. Hysteria sometimes simulates hydrophobia quite closely, especially in cases

where the patient has been bitten by a dog and has been anxious about it. In these instances there may be general convulsions with constant barking and biting. A careful review of the history and symptoms, and especially the absence of the respiratory spasm, will usually make the diagnosis clear.

The differentiation from mania may be difficult at first, and must depend largely on the history. The rapid course of the disease will soon clear up the diagnosis. As Gowers says, "No patient ever passed from mental health to a state of imminent danger in two or three days in consequence of simple insanity."

Lyssophobia is the name given to a series of symptoms which are sometimes seen in nervous persons who have an exaggerated fear of hydrophobia. Autosuggestion determines spasms in the throat on swallowing, and a dread of water may follow in consequence. The symptoms usually occur soon after the bite, sooner in fact than the shortest period of incubation in the true disease. There is lacking also the true respiratory spasm, and the patient can usually be quieted. It has not been proved that death ever takes place from lyssophobia.

Prognosis.—Reported instances of recovery at best are so rare that a fatal outcome must always be looked for. In dogs a few well-authenticated instances of recovery following inoculation have been reported.

The prognosis as regards bites by rabid animals depends, as has been stated, on the animal inflicting the bites, the size, number, character, and location of the wounds; also on the length of time between the injury and cauterization, and on the thoroughness with which it is done. When done properly and thoroughly the protection is very great—in moderate wounds practically absolute. The statistics of Proust show that, in a series of 117 cases, which were not cauterized, there were 96 deaths; while among 249 cases, in which cauterization was practised, only 89 deaths occurred. When the wounds are multiple and lacerated, and especially when about the face and head, thorough cauterization is difficult or impossible.

The outlook is most favorably influenced by the Pasteur treatment. At the parent Institute up to January, 1904, 27,719 cases of all descriptions have been treated, with 117 deaths, a mortality of 0.42 per cent. These figures exclude a small number of persons in whom the disease appeared during or within fifteen days after treatment.

As in other methods of vaccination, immunity is produced only after a certain lapse of time, and in cases of short incubation, or of late commencement of the treatment, the disease may manifest itself before the vaccinal effect has been procured. For this reason certain cases of death are justly excluded from the statistics of the Pasteur treatment. Their admission would, however, raise the percentage very little. The work of Krauss and Kreissl throws much light on the production of immunity by the Pasteur treatment, and emphasizes the importance of beginning treatment promptly. These authors find that the serum of healthy men, as a rule, does not contain any protective property against the virus of rabies, nor is any found immediately after the completion

of vaccination, but twenty-two days later marked antirabic power is present, and is retained for a long time. Cases in which the treatment is unsuccessful are probably due to the absence of this property. It is important that the treatment be begun within one week of the bite. Statistics collected by Högyès, including 54,620 persons treated at 24 institutes, show that the total mortality was only 0.77 per cent.

In Hungary, where rabies is very prevalent, from 1890 to 1895, there were 5899 persons bitten, of whom 4914 received the Pasteur treatment, with a mortality of 1.2 per cent., while among those not treated 14.94 per cent. died of rabies.

Treatment.—When the disease has declared itself, this is purely palliative, and directed to relieving so far as possible the suffering of the patient. Our efforts must be directed to preserving the strength, and lessening the frequency of the paroxysms. Every source of annoyance should be removed. The room must be darkened, warm, and quiet. Only the necessary attendants should have access to the patient. Especially must draughts of air and sharp noises be avoided. The diet should be as concentrated as possible, and liquid. Osler advises the use of cocaine to the fauces to facilitate the taking of liquids. If the dysphagia is marked, recourse must be had to rectal enemas. Thirst must be relieved by the same measures.

The list of drugs which have been recommended is a long one. None have any specific value. Hypodermic injections of morphine and inhalations of chloroform will generally give more relief than any other drugs. They should be used from the beginning, and no time wasted in giving the milder antispasmodics. Calabar bean and curara have been recommended. Three cases of cure are credited to curara, one of which Gowers considers "undoubtedly genuine." As it acts by paralyzing the motor nerves, artificial respiration may become necessary.

Forcible restraint during the paroxysms is often required. Tracheotomy has been advised, but is useless, since the dyspnœa is due to spasm of the respiratory muscles, and the glottis is not closed.

Preventive Treatment.—The bite of any suspicious animal should receive prompt attention. The invariable rule must be: Cauterize as soon as possible and in the meantime do everything to get the virus out of the wound and prevent its absorption. Open the wound freely so that every part of it can be exposed. Encourage bleeding by cupping or suction with the lips, the mouth being well washed after each application. Bathe abundantly, preferably with tepid water. If the wound is on a limb, a ligature may be applied above the site. As soon as possible the wound must be thoroughly cauterized. For this purpose fuming nitric acid is the best agent. It must be applied to every portion of the wound with a fearless hand, deep punctures having previously been laid open with the knife. In the absence of nitric acid, lunar caustic, the actual cautery, or strong antiseptics should be used. The importance of early and thorough cauterization cannot be overstated. There is strong experimental evidence that laying open the wound and the free use of nitric acid will save a certain proportion of cases even after a lapse of twenty-four hours. It should never be neglected, since it retards the

development of the disease, and thus renders the Pasteur treatment more certain of effect.

Pasteur Method of Immunization.—Pasteur observed that by residence in the nervous system of certain species of animals the power of the virus was exalted, while, on the contrary, by residence in other species it became attenuated. By inoculation of rabbits in series, one from the other, we obtain a virus of greatly increased virulence, so that after about one hundred passages they will die with great regularity on the sixth or seventh day. Beyond this point no increase of virulence can be obtained, therefore Pasteur gave it the name "fixed virus" in order to distinguish it from that found in dogs under natural conditions, which is known as "street virus." On the other hand, when monkeys are inoculated in series, the period of incubation becomes gradually lengthened, until after a time the virus becomes so attenuated that it no longer causes death. With the assistance of Chamberland and Roux the method in universal use was worked out, depending on the fact that the rabic virus contained in the spinal cords and brains of rabbits becomes attenuated fairly evenly and regularly by drying when protected from putrefaction, so that it is harmless at the end of fourteen or fifteen days. The method is carried out as follows: Rabbits are inoculated subdurally with the fixed virus daily. At death, the spinal cord is removed with strict aseptic precautions, cut into three pieces, and suspended in large bottles containing a layer of caustic potash. These bottles have an opening near the bottom as well as at the top, both of which are plugged with cotton, so as to allow free passage of air. They are kept in a dark room at a constant temperature of 23° C. Thus, a full series of cords from fourteen days up to one day old is at hand, giving various attenuations of the virus from the weakest to the strongest. The usual dose is a portion of cord 2 to 3 mm. in length, which is prepared for injection by trituration and suspension in normal salt solution or bouillon.

As practised today at the Pasteur Institute in Paris, the treatment is modified according to the urgency of the case. We have thus a "simple" treatment, lasting fifteen days, employed where the bites are slight; the ordinary treatment, extending over eighteen days, for cases of bites about the hand, limbs, etc.; and an "intensive" treatment, which requires twenty-one days, applied when the bites are about the face and head and a short incubation period is reasonably to be expected.

Calmette's Modification.—The method of preparing the vaccines as given above requires a large number of animals and much attention, and is too expensive unless the number of patients treated is very large, which is seldom the case. Calmette has introduced a modification generally adopted in smaller institutes and found to be very successful. The requisite number of rabbits are inoculated with fixed virus every tenth day. The cords are removed at death, suspended over caustic potash, and placed in the drying chamber. After forty-eight hours, a portion of a cord is cut off and placed in sterile glycerin contained in glass-stoppered bottles. The operation is repeated each succeeding day until the fourteenth. It has been shown that cords so preserved retain their virulence unchanged for twenty-five to thirty days. In this

manner the full series of vaccines is always on hand. Inoculations are begun with cord desiccated for fourteen days, and preserved twenty to twenty-five days in glycerin. During the last four days cords are used which have been in glycerin for five to ten days. The dose is a section of cord 3 mm. to 5 mm. in length, made into an emulsion.

Other Modifications.— Cummins uses fixed virus modified by dialysis. Harris subjects the virus to vacuum desiccation while frozen. Semple makes an 8 per cent. dilution of the virus in normal salt, to which 1 per cent. of carbolic acid is added, and the mixture kept at 37° C. for twenty-four hours. This destroys its vitality. It is then diluted with an equal amount of normal salt solution. This has proved so satisfactory in producing immunity experimentally that it has been officially adopted in the Indian Pasteur Institutes.

The original scheme of injections as devised by Pasteur has been greatly modified. Pasteur began with fixed virus which had been dried for fourteen days, and never gave a more virulent cord than one dried for three days. Experience has shown that fixed virus is greatly modified in its virulence for man, and that it is not necessary to begin with such extreme attenuations. In fact, Ferran, Proescher, and others use unmodified fixed virus in quite large doses. In Germany the treatment begins with virus dried only three days, and is followed on succeeding days by cords dried for two and one day. At no time during the twenty-one days of treatment is a milder virus employed. In America, the scheme of the Public Health Service is largely followed, beginning with cords of the eighth day and proceeding rapidly to those of the third, second, and first day.

Scheme for Intensive Treatment

Day	Cord	Amount		
		Adult	5 to 10 years	1 to 5 years
1	8–7–6	2.5 cc.	2.5 cc.	2.5 cc.
2	4–3	2.5 cc.	2.5 cc.	2.0 cc.
3	5–4	2.5 cc.	2.5 cc.	2.5 cc.
4	3	2.5 cc.	2.5 cc.	2.0 cc.
5	3	2.5 cc.	2.5 cc.	2.0 cc.
6	2	2.5 cc.	2.0 cc.	1.5 cc.
7	2	2.5 cc.	2.5 cc.	2.0 cc.
8	1	2.5 cc.	1.5 cc.	1.0 cc.
9	5	2.5 cc.	2.5 cc.	2.5 cc.
10	4	2.5 cc.	2.5 cc.	2.5 cc.
11	4	2.5 cc.	2.5 cc.	2.5 cc.
12	3	2.5 cc.	2.5 cc.	2.0 cc.
13	3	2.5 cc.	2.5 cc.	2.0 cc.
14	2	2.5 cc.	2.5 cc.	2.0 cc.
15	2	2.5 cc.	2.5 cc.	2.0 cc.
16	4	2.5 cc.	2.5 cc.	2.5 cc.
17	3	2.5 cc.	2.5 cc.	2.5 cc.
18	2	2.5 cc.	2.5 cc.	2.0 cc.
19	3	2.5 cc.	2.5 cc.	2.0 cc.
20	2	2.5 cc.	2.5 cc.	2.5 cc.
21	1	2.5 cc.	2.5 cc.	2.0 cc.

The Pasteur treatment should always be begun as soon after the bite as possible. It is useless after the symptoms have declared themselves. The probabilities of failure are least in those who present themselves for treatment during the first week, since only those in whom the period of incubation will be less than twenty days will fail to receive immunity. The usual incubation exceeds this time considerably. It has been abundantly shown experimentally, as well as by comparative mortality tables, that the period of incubation is lengthened in persons who succumb after partial or complete treatment.

Effect of Treatment.—In the vast majority of cases no ill effects follow the injections, even when not needed. At the present, 76 cases with 4 deaths have occurred.[1] According to Jones,[2] who has reported the only cases from America, the symptoms, especially in severe cases, are not unlike those of Landry's paralysis, or a severe multiple neuritis. In milder cases, "flashes," numbness, and more or less paralysis are observed. Most cases recover spontaneously. The cause is not understood. It is believed by Roux, Koch, and others that the symptoms are due to the virus introduced by the bite which is so modified by the attenuated fixed virus as to produce an abortive or atypical rabies ending in recovery. By others the fixed virus, or its contained toxin, is held responsible. Harvey and McKendrick[3] regard the symptoms as anaphylactic phenomena.

Duration of Immunity.—We have no statistics on this point for man. It has been studied in dogs, in whom the protection has been found to have disappeared in 21 per cent. at the end of one year, in 33 per cent. after two years, while in others it has persisted for five years. Persons bitten a second time by a rabid dog should again receive treatment, unless a very short time has elapsed.

Serum Therapy.—Serums obtained from immunized animals have been used, but while the experimental results in the production of an antirabic serum are encouraging, its use has not gained headway practically.

Prevention.—Rabies is a preventable disease. Since more than 90 per cent. of all cases are due to bites from dogs, and since it is kept alive in the canine race, our measures must be directed to the control of these animals. It is better and more humane to have them under supervision than to subject them to the extreme measures sometimes enacted during the terror which reigns in a community in which an outbreak of rabies occurs. The wholesale destruction of dogs sometimes seen is cruel and wholly unnecessary. Among the measures proposed for the control of dogs may be mentioned high tax, muzzling, and the leash, with the destruction of homeless and wandering animals. The results of muzzling justify its recommendation, and there is little doubt that its strict enforcement will eradicate rabies from any community in a short time. Great Britain furnishes a striking example of its efficacy. In 1887 there were 217 cases of rabies in Great Britain; in 1888, 160; and in 1889, 312. The increase caused alarm and muzzling was enforced, as

[1] Stimson, *Hygienic Lab. Bull.*, 165.
[2] *Jour. Am. Med. Assn.*, 1909.
[3] *Theory and Pract. Antirabic Immun.*, Calcutta, 1907.

a result of which in 1890, 129 cases were seen; in 1891, 79 cases; in 1892, 38 cases. There was much opposition to muzzling and the ordinance was relaxed. In 1893 the number of cases rose to 93; in 1894, to 248; and in 1895, to 672. Muzzling was again enforced, resulting at once in a marked decrease of cases to 438 in 1896, 151 in 1897, 17 in 1898, 9 in 1899, and none in 1900.

More remarkable still are the results which have been obtained in the Department of the Seine. The repressive measures have consisted largely in the destruction of stray dogs and a dog tax. In 1900 there were 637, and in 1901, 623 patients treated at the Pasteur Institute in Paris; in 1909 only 105. There has been no death from rabies in the Department of the Seine since 1904. These results are all the more striking when we remember the statement of Nocard that "the Department of the Seine was a focus of infection unique in the world." They furthermore effectually dispose of the often repeated claim of the antivivisectionists, that Pasteur Institutes spread hydrophobia.

CHAPTER XXXI

RHEUMATIC FEVER

By FREDERICK J. POYNTON, M.D., F.R.C.P. (Lond.).

Etiology.—*Rheumatic fever* takes a very prominent position among the diseases of temperate climates, and has from ancient times attracted much attention. As a result of modern investigation the writer believes that he may safely assert that it is an infective disease and that references to the older theories of its origin may be omitted. In taking this step the writer fully recognizes that the earlier investigators provided invaluable material for our present knowledge. Such a step is but the forward movement that is dependent upon progress, and doubtless in the future will in its turn serve but as another resting place from which further advance may be made.

When we investigate the reasons for looking upon rheumatic fever as infective, we find the most convincing evidence in every direction. To quote the late Dr. Cheadle's words upon this point: "The occasional epidemic prevalence, the variability of type, the incidence upon the young, the occurrence of tonsillitis, of endocarditis, of pneumonia, of erythematous eruptions; the rapid anemia, the tendency to capillary hemorrhage and albuminuria; the implication of the joints, the relapses, the occasional supervention of hyperpyrexia, the nervous disturbance, the specific power of salicylic acid, are all suggestive of an infectious disease." The pathological and bacteriological facts in support of this view are also most convincing.

The exact nature of the infection, however, has led to much controversy, and at the present time there is no general agreement upon this point. A study of the morbid anatomy of rheumatic fever points to its classification among the diseases that result from micrococcal infections; that is to say, with the diseases that result from infections with streptococci, staphylococci, and pneumococci. The several views upon the present position are as follows: (1) That there is no specific microörganism, but the disease is a form of septicemia which owes its origin to staphylococcal or streptococcal infections. (2) That the disease is due to a specific bacillus. (3) That the microörganism is a diplococcus. (4) That the exciting cause is as yet unknown.

The *first* view, that the disease is an attenuated pyemia, is one very widely held. Yet at the present time, in the writer's opinion, those who hold it have never established their position, and to it there are obvious and grave objections. In the first place rheumatic fever is a very common disease—far more common than the various forms of pyemia; yet it is most exceptional to find that it arises in connection

with pyemia. Now and again there are puzzling cases which follow otitis media or a tonsillar abscess which to some extent support this view. Yet for one of these, hundreds of cases of rheumatic fever arise in such a way and run such a course that they cannot be grouped as examples of attenuated pyemia, without making an assumption not justified by facts.

No value can be attached to the statement, commonly made, that rheumatism is a form of septicemia. Any infection, if sufficiently severe, will cause a septicemia, and a vague statement such as the above gives no real assistance toward the proper understanding of the disease.

Again, rheumatic fever can be most deadly. What more terrible poisoning can be found than a severe attack with hyperpyrexia? This is certainly not an attenuated infection, and it certainly is not pyemia. Lastly, because various micrococci, including the staphylococcus aureus, have been found in the tissues and isolated from them in rheumatic fever, this does not constitute a proof that they are a cause of the disease; or because various micrococci have produced arthritis and endocarditis in animals, this is no proof that they are therefore the cause of rheumatic fever. Many infections in man will cause arthritis or endocarditis and yet the condition need not be rheumatic fever. The cardinal rules of investigation must be followed; that is to say, a microörganism must be found with constancy in the important lesions of the disease; it must be isolated and cultivated outside the body; it must produce similar lesions in susceptible animals and must be again isolated from these lesions. No proof short of this suffices; and until this proof has been obtained for more than one micrococcus the view that various attenuated micrococci are causes of rheumatic fever is not established.

The *second* of the these views, which looks upon the disease as the result of an infection with a specific bacillus, is not substantiated. A large bacillus was indeed found by Achalme in 1891, and later other French observers, in particular Thiroloix and Rosenthal,[1] who state that they have reproduced experimentally the rheumatic lesions. They further hold that this bacillus which grows anaërobically will if grown aërobically alter into a diplococcal form in a less favorable medium. The English investigations have failed to confirm these results, and it seems impossible that the bacillus, described as of a size equal to that of the anthrax bacillus, can have been overlooked by many observers.

The *third* view maintains that the cause is a diplococcus belonging to the group of streptococci allied to the *Streptococcus pyogenes* on the one hand and to the *Pneumococcus lanceolatus* on the other. This diplococcus had been isolated by a considerable number of investigators and its relationship to the disease worked out step by step within the last sixteen years. Triboulet and Apert in 1898 placed the position of this diplococcus upon a firmer basis by producing mitral disease in a rabbit by an injection of the microörganism obtained from the blood of a patient with rheumatic fever. Westphal, Wassermann, and Malkoff, in 1899, produced fever and multiple arthritis in eighty rabbits with

[1] *Gazette des Hôpitaux*, October 19, 1907.

a similar microörganism, obtained from a fatal case of rheumatism. Paine and the writer in 1900 published the results of an independent investigation in which they isolated this diplococcus from 8 successive cases of rheumatic fever and showed its presence in the most important human lesions; they produced these various lesions in rabbits and isolated the diplococcus from the animal tissues. Since that date they have increased the number of cases from 8 to 75 with only occasional failures.

The results of experiments are on the whole remarkably constant, and the reader cannot lose sight of the fact that a microörganism which is present in the lesions of rheumatic fever is capable of reproducing similar lesions in animals. Vernon-Shaw in 1903 demonstrated that monkeys were susceptible to the infection with a culture obtained by the writer from rheumatic pericarditis immediately after death. Fritz Meyer, Ainley Walker and Beatson, Beattie, Longcope and Lewis, Bracht, Wachter, Coombs Miller and Kettle, and Rosenow have confirmed many of the observations and have added more facts.

Rosenow has to a large extent confirmed these views. He has obtained organisms corresponding to the *Micrococcus rheumaticus* from the joints, blood, tonsils, and periarticular tissues of patients with rheumatic fever. In animals multiple non-suppurative arthritis, endocarditis, and myocarditis were obtained repeatedly; the joint lesions produced were chiefly periarticular. Changes occurred in certain of the strains by animal passage and other means; for example, one strain lost much of its affinity for the endocardium, pericardium, and articular tissues and acquired what seemed to be an affinity for the myocardium, skeletal muscles, and the kidney, producing a non-suppurative myocarditis, myocarditis, and acute nephritis. The lesions produced in the muscles were most numerous in the tendinous portions of the muscles of the extremities, the flat muscles about the neck and shoulder, the intercostal muscles, and the muscles of the spine. The various strains resembled closely *Streptococcus viridans* and hemolytic streptococci culturally and morphologically, but behaved quite differently on injection into animals.

The chief characteristics of the microörganism are: It is a small micrococcus 0.5μ in diameter, and usually grows in pairs or in short chains. As a rule it does not show a capsule, but there is reason to believe that in the human tissues the appearance of capsulation may be occasionally found. It stains readily with aniline dyes. Some writers have stated that it retains Gram's stain; this is undoubtedly correct; but it does not retain this stain with great tenacity.

Degenerative forms are common, and the micrococcus then becomes swollen or pear-shaped. Some discussion has arisen over the name that should be given to it, but there seems no good reason for altering the name that Paine and the writer originally gave to it in 1901—the "Diplococcus rheumaticus," for it will be found in the majority of instances as a diplococcus rather than a streptococcus, and it is a cause of rheumatic fever. If a descriptive name is needed the "Diplococcus rheumaticus" is the most accurate—if a family name is required then "Streptococcus rheumaticus."

Cultural Characteristics.—*In bouillon* at 37° C. there is in twenty-four hours turbidity with slight flocculent deposit. In three days the fluid becomes clear and there is a distinct deposit. The medium becomes acid. *Gelatin (Stab)*: In forty-eight hours minute colonies appear along the track of the needle; there is no liquefaction. *Blood agar:* This medium is one of the most favorable. Fresh blood is smeared upon the agar, and incubated for twenty-four hours. In twenty-four hours after inoculation minute white colonies are visible; these tend to remain discrete and alter the blood pigment to a rusty brown color. A noteworthy point is the remarkable vitality of the microörganism upon this medium, and it is interesting to record that the original culture isolated by Paine in 1899 is still growing in subculture. *Milk and bouillon* (equal parts) slightly acidified with lactic acid. This medium is a most serviceable one for isolation of the microörganism. In twenty-four hours the milk is coagulated. *Litmus milk* (blue) is turned a pinkish tint in forty-eight hours and the milk coagulated. Vernon-Shaw found that the best medium was glycerin, veal broth containing 2 per cent. peptone, and 1 per cent. alkaline to phenolphthalein. Beattie finds a definite and very distinctive reaction in the production of acid and precipitation of the bile salts in McConkey's bile salt lactose broth.

A feature of this microörganism is the power it possesses of producing acid. Although a production of acid is a property common to many bacteria, this one possesses the power in a marked degree. Triboulet and Coyon, Walker and Ryffel, Shaw and Berger, have investigated these acids, and it is clear from their investigations that they vary with the medium in which the microörganism is grown. Walker and Ryffel have directed attention to the large quantity of formic acid that the microörganism forms, and have extracted it from the bodies of the microorganisms themselves. Further investigations can alone show how much specific value we can attach to this formation of formic acid. In any case, however, it is a very interesting point that an acid which produces such an irritant effect upon the tissues should be formed in considerable quantity

Much controversy has arisen over an attempt to separate this diplococcus from other streptococci by means of certain fermentation tests *in vitro* with various sugars, but such results do not appear to the writer to affect the evidence that this diplococcus is a cause of rheumatic fever as some would seem to suggest. Whatever may happen *in vitro* in sugar media, with such microörganisms as streptococci, need have no bearing upon their reactions when pathogenic in the human body, and if those reactions could be used as tests *in vitro* an entirely different classification of streptococci might result. Whether the diplococcus is or is not allied to various streptococci appears to the writer to have little meaning. Nevertheless, he is keenly alive to the value of any investigations that may differentiate the streptococcus more effectually, although absolutely opposed to the argument that failure in this direction alters the main issue—the cause of rheumatic fever.

Although it is sometimes a difficult matter to demonstrate them, the diplococci are probably present in all the chief rheumatic lesions.

At one time or another they have been demonstrated in the endocardial and pericardial tissues, in the pleuræ, peritoneum, pia mater, synovial membranes, nodules, lungs, urine, and blood,

In this article as elsewhere the writer has purposely avoided the use of the term "specific" as applied to the "Diplococcus rheumaticus;" and the present position of the etiology appears to him to be this: Rheumatic fever is a *specific disease*, and so far as our knowledge goes owns but one exciting cause, variously called a diplococcus, streptococcus, or micrococcus. The bacteriologist would wish, perhaps, to go further and say that this diplococcus is specific; such may prove to be the case, and is probable; but the discovery of a specific test for a microörganism is a different matter to establishing it as the cause of a specific disease.

The *fourth* and last view, which maintains that the exciting cause has yet to be demonstrated, rests upon the interpretation put upon experimental investigations with various streptococci derived from sources that were not rheumatic, and upon the fact that the micrococcus of rheumatism is very rarely found in the acute synovial exudations and blood of man. Many investigators, and notably Cole and Rosenow, have shown that various streptococci may produce an endocarditis and arthritis in rabbits indistinguishable from that produced by the microörganism of rheumatism.

To the writer, who has also studied the results of various streptococci, such an interpretation has these objections: It is not admissible to omit the first two of the cardinal laws of investigation, and to use experimental results with micrococci which have not been obtained from cases of rheumatic fever, as evidence for or against the cause of the disease. Such a procedure involves the assumption that lesions which have a superficial resemblance to one another are identical and is a very dangerous one. In man, for example, early endocarditis, whether pneumococcal, rheumatic, staphylococcal, or tuberculous in causation, has much the same superficial appearance; yet the diseases are widely different. It is difficult, moreover, to explain away the fact that a microörganism which has been repeatedly *isolated from the lesions of rheumatic fever* should produce with remarkable constancy the lesions of that disease in animals, and that these lesions should occur not only in rabbits but also in monkeys.[1]

This view would perhaps have had more weight if rheumatic fever in man was the only cause of endocarditis and arthritis; but it is well known that many allied but not identical diseases produce these effects in man as well as animals. Little value, again, can be attached to the negative results that have been obtained from investigations of the blood and synovial exudations in rheumatic fever.

Heredity is admitted as a very important predisposing cause, and in studying a long series of cases one cannot but be struck by the great

[1] Some bacteriologists have suggested that the diplococcus occurs as a terminal infection. There is a patient living now and in active work from whose blood Paine and the writer isolated the diplococcus thirteen years ago during an attack of acute rheumatic pericarditis. They have also isolated it from the arthritic exudate and cerebrospinal fluid during life, as have other investigators. This objection can be finally dismissed by the further observations of Beattie and Yates.

frequency with which a family history of the disease is obtained after all allowance has been made for the vague use of the word "rheumatism." A distinction should be drawn between the "rheumatic diathesis" and those rare cases in which the mother suffered from rheumatic fever during pregnancy and the child is born with active carditis. In these cases there is probably a direct infection through the placental circulation.

The following analysis from the late Dr. Cheadle's private records illustrates the influence of heredity. In 32 consecutive cases, in 23 or 70 per cent. there was a definite history of rheumatic fever in near blood relations. If chorea and erythema are taken as sufficient evidence, the proportion was raised to 31 out of 33, or 93 per cent. If all the cases of arthritis, chorea, and morbus cordis were taken together, of 180 cases 103 gave a definite family history (58 per cent.).

Age.—Rheumatic fever is rare under five years of age, but from that time up to fifteen its frequency greatly increases; throughout adult life it is met with, but in advancing years the tendency diminishes considerably. It is an error to suppose that this disease occurs more frequently in adult life than in childhood.

Sex.—Allowing that the male adult is more exposed to sudden chills and severe exposure by virtue of his occupation, there is no striking difference except in childhood. At this age the disease is more frequent in females owing to the far greater number of cases of chorea.

Climate, Season, and Locality.—The disease is ubiquitous, but is more frequent and severe in temperate and changeable climates. The majority of cases occur in autumn and spring; the fewest occur in summer; but they are met with all the year around. It is essentially an urban disease, favored by cold winds and damp. Newsholme associates it with a low level of ground water; in London, it is more rife and more severe when the cold and rain of autumn follow a hot, dry summer. Damp alone does not explain its frequency, if—as seems to be the case—it is true that it is an urban disease and more severe when the subsoil water-level is low. Often there is no convincing history of chill or damp, but there can be no doubt that exposure to damp cold increases the severity and persistence of rheumatic fever, a point which Beattie has proved in the experimental arthritis of rabbits.

Epidemics.—There is a good deal of evidence to show that there are waves of rheumatic fever; and, in addition, the character of the disease alters in different outbreaks. Closely allied to epidemic occurrence is the possibility of spread by contagion, and some remarkable examples have been recorded. There are nevertheless difficulties in establishing the truth of this—partly owing to the strong hereditary tendency,and partly to the probable influence of atmospheric conditions. It is not uncommon to find that two and even three children in a family are simultaneously attacked, but this does not prove contagiousness.

Diet.—This does not appear to have any marked effect, and it seems improbable that an excess of meat or carbohydrate is a cause. Excess of uric acid has no immediate bearing on the causation.

Infectious Diseases.—It is possible that an infectious disease associated with sore throat, such as scarlet fever, measles, or diphtheria, may predispose to the rheumatic fever infection.

Pathology.—The pathological changes are for the most part easily understood. The exact nature of the changes produced by the toxins cannot, it is true, be demonstrated, but the macroscopic and microscopic appearances are quite explicable. The lesions, the carditis, arthritis, nodule formation, pleurisy, etc., are primarily due to the local deposition of the bacteria, and not the result of toxins only. The bacterial infection is widespread and not localized.

The entire question of the morbid anatomy has assumed a different complexion since Aschoff and Tawara, Carey Coombs, and Fraenzel have maintained that certain of the lesions—the submiliary nodules—are peculiar to the disease in that they show a special structure which Coombs, Miller and Kettle have recently reproduced experimentally in rabbits. These scattered foci are found in the various tissues affected. The nodules consist of fusiform areas formed by large spindle-shaped cells lying in the intermuscular trabeculæ of connective tissue. These cells are larger, but otherwise resemble fibroblasts and are often multinuclear. Around their periphery are found plasma cells and mononuclear leukocytes. These nodules are slowly replaced by connective tissue. The writer has confirmed these special appearances, but he would deprecate any attempt at present to look upon them as specific tests of the disease without the presence of which we cannot accept any other evidence, a view held by Fraenzel. Such a step is but to substitute a single anatomical feature for the broad scientific lines upon which the etiology of the disease is based.

From this infection three types of injury result.

1. The simple type. (2) The fibroid type. (3) The malignant type.

1. In the *simple* type, which is illustrated by acute rheumatic arthritis, the bacteria are rapidly destroyed by the resistance of the tissues, and the resulting inflammation quickly subsides. If the infection is more severe, or the resistance imperfect, death of some part of the affected tissues will occur, and with resolution this dead tissue is replaced by scar formation. The thickening of the mitral valve after acute simple endocarditis illustrates this repair.

The microscopic changes are dilatation and sometimes rupture of the blood capillaries, with well-marked swelling of the connective tissues in their neighborhood. Where the process is most severe the connective tissues pass from the stage of swelling to that of necrosis and the area is invaded with leukocytes. With resolution fibroblasts invade the necrotic area and thus a scar is formed. When these changes occur in the subendothelial tissues of a serous membrane, such as the synovial, pericardial, or pleural, there is a rapid exudation into the serous cavity of a clear or blood-stained fluid which later becomes serofibrinous. It is often said that suppuration does not occur in rheumatic fever, and this is true if the term suppuration is restricted to the yellow fluid found in pyemic abscesses, empyema, etc. In severe rheumatic peri-

carditis, however, the condition is in the author's opinion to all intents a *rheumatic* suppuration.

The relation of the bacteria to the exudations is interesting and easily understood; yet their absence from the early exudations has more than any other single fact influenced investigators against the bacterial origin of the disease. The diplococci escaping from the minute blood capillaries are necessarily at first located in the subendothelial tissue, and the endothelium serves as a bar to their escape into the serous cavity. The rapid destruction of the diplococci by tissue cells can be well seen in the wall of the appendix in experimental rheumatic appendicitis. For this reason there is great difficulty in finding them in acute effusions into the joints or other serous cavities. Later, again, when after a severe infection their poisons have destroyed the protective endothelium and they have escaped into the serous cavities, the leukocytes attack and destroy them. The particular phase in which the bacteria can be easily obtained is the comparatively rare one in which many have escaped into the fluid and the leukocytes have failed or have not had time to destroy them.

2. The *fibroid type* of lesion is best exemplified by mitral stenosis. For some reason, as yet unexplained, this type is more frequently found in the female sex. It is a subacute inflammation very persistent in character, which without causing any considerable amount of necrosis produces a gradual sclerosis. It may be objected that no line of demarcation can be drawn between the simple and fibroid type of inflammation; but there is this practical value in the recognition of them, that it brings into prominence the difference in the prognosis and emphasizes the persistent nature of the fibroid type of the disease.

3. The *malignant* type is best exemplified by certain cases of rheumatic endocarditis in which the microörganisms are not destroyed in the tissues but multiply in the damaged valve and are then disseminated by the blood stream. In the most severe form the vegetations are minute, and yet there are immense numbers of bacteria in them; in those of less severity there are large fungating vegetations in which many bacteria may be present, but in which many are destroyed.

The intimate changes produced by the rheumatic toxins are not known; but one condition is clearly recognized, namely, fatty degeneration. This is sometimes well-marked in the cardiac muscle and also in the convoluted tubules of the kidneys when they are severely attacked. Beattie has found amyloid degeneration in 4 cases. The changes in the nervous tissues in rheumatic chorea are not as yet thoroughly determined. Gordon Holmes and the writer have investigated 3 cases of fatal chorea and found (1) the diplococcus in the pia mater and brain; (2) vascular and inflammatory changes in the central nervous system and its membranes; (3) changes in the nervous tissue itself, some destructive and secondary to the vascular changes, others due to alteration in the morphological characters of the nerve cells. Fraenzel has demonstrated submiliary nodules in the pia mater.

General Symptoms.—Onset.—This, especially in childhood, differs widely in its characters. Thus it may be insidious and preceded by indefi-

nite illness, which can be compared to the gradual failure of health that so frequently precedes acute tuberculosis. The following symptoms are met with, among others, in this prodromal stage: anemia, nervousness, irritability, epistaxis, loss of energy, wasting, headache, sore throat, epigastric pain, and fleeting pains in the joints. The temperature is usually above the normal, *e. g.*, 99.5° F.

Children of rheumatic stock may complain of these indefinite symptoms for long periods before they are attacked by acute symptoms, as for example, in the case of a little girl who was under the writer's care for four years and during that time continually showed one or other of these symptoms. After being chilled, a sore throat followed and after this chorea and mitral endocarditis; since that time she has had several definite attacks of rheumatic fever. The manifestation which commences in this insidious way is most frequently chorea.

When the onset is acute, there may be some definite history of chill or exposure from which the illness is dated, and the first symptoms generally show themselves within a week of this. In the child these are generally sore throat, malaise, fever, pains in the limbs, and prostration. In the more virulent cases shivering, vomiting, and diarrhœa may occur. The symptoms vary in accordance with the organs chiefly attacked; thus multiple and painful arthritis, as in the adult, may be the prominent symptom, or chorea, precordial pain, and dyspnœa. In severe attacks several manifestations may develop within a few days. In some rare cases the subcutaneous nodules have first attracted attention; in others, an eruption.

In the adult the disease may commence in the same insidious manner as in the child; but the acute articular disease is more usual, and when fully developed is characteristic. There may be sore throat, chilly feelings, or even a rigor, and, with these, general malaise, muscular pains, and weakness, The arthritis sometimes appears with great rapidity. There is profuse sweating which is rarely seen in the child, and the sour odor arising from this has long been pointed out as a feature of the disease. If there is excessive sweating a sudaminal rash not infrequently appears on the trunk. The sufferer lies in bed, quite helpless and dreading any movement; many of the larger joints and sometimes the smaller ones are swollen and extremely tender. There may be a red flush over the articulations most severely attacked, and the implication of the tendons and periarticular tissues adds greatly to the distress. Another feature is the rapidity with which the inflammation passes from joint to joint, and also the rapidity with which recovery may occur. Neither in children nor adults is there any characteristic fever. The temperature is moderately raised, 100° to 102° F., and often higher in the adult than in the child. In severe cases the temperature may oscillate considerably in the twenty-four hours. A manifestation which is apt to raise the temperature considerably is a patch of bronchopneumonia.

When much fluid is lost through sweating there is considerable thirst, the appetite is poor, and the bowels constipated. The pulse is usually more rapid than normal and the wave large and easily compressible, and both in adults and children dilatation of the heart is common. The

mind is clear and as a rule acute; not infrequently there is anxiety, mental distress, and insomnia, from the pain. The respiratory system is not usually damaged. The urine is scanty, high colored, and strongly acid; the chlorides are diminished and the urates increased. Hematoporphyrin is sometimes present in considerable quantities.

The interesting question has been raised as to whether rheumatic fever in childhood is the same disease as that which is found in adult life. In the last sixteen years the writer has followed many patients in whom fresh attacks have occurred in adult life who were also victims in childhood and has convinced himself of the identity of the affection.

Course.—There are few diseases which run a more variable course. In children it is impossible to give any definite rule, for it will greatly depend upon whether the heart is damaged. Then, again, in children virulent cases occur which are never very acute, but which on the other hand never subside; week after week, month after month, one manifestation after another appears, and when death ensues, many months later, it may be truly said that the child was never free from the disease after the onset of symptoms. How closely this recalls the course of a chronic generalizing tuberculosis in childhood need hardly be insisted upon. Nevertheless, there are many cases in which, as in adults, the acute symptoms have entirely disappeared in three weeks. In the adult it is the frequency of the articular type that gives a more uniform character to the disease. Yet even in this type there is the same tendency to recrudescence of the symptoms—or, as they are generally termed, to relapses—which may protract the illness over many weeks. A fatal termination is fortunately rare; when it occurs the most usual cause is acute heart disease; but the most fatal complication is hyperpyrexia.

In this general description no separation has been made, as is so often done, between the disease in the adult and in childhood; for this gives an imperfect idea, more especially because it has been the custom to write of the disease in the adult as if it were the type. Nevertheless there is much practical value in due recognition of the special features in childhood, and these are put in tabular form:

1. The onset is frequently insidious, with a prodromal stage in which lassitude, anemia, epistaxis, and epigastric pain, etc., occur.

2. The manifestations are more varied, and the invasion is more general in the child. The most frequent of these manifestations are (*a*) chorea; (*b*) articular pains and swelling; (*c*) tonsillitis; (*d*) carditis; (*e*) erythema multiforme; (*f*) pleurisy and pneumonia; (*g*) subcutaneous nodules.

3. The occurrence of heart disease is more frequent than in the adult, and for this reason the disease is more fatal in childhood.

4. Articular complications, though frequent, are less severe.

5. Sweating is less common.

6. Nervous symptoms are more often met, notably chorea; but hyperpyrexia is less frequent.

7. There is a greater tendency for the child to drift into the rheumatic state.

8. Subcutaneous nodules are much more common.

9. Malignant rheumatic endocarditis is less common.
10. The anemia is often more profound.

After this preliminary account of the general symptoms it is necessary to study in more detail the important visceral lesions which are considered under the following headings:

1. Those connected with the cardiovascular system.
2. Those connected with the joints, muscles, tendons, and fasciæ.
3. Those connected with the nervous system.
4. Those connected with the respiratory system.
5. Those connected with the cutaneous system.
6. Rarer manifestations: (i) alimentary, (ii) genito-urinary, (iii) miscellaneous.

It may be of assistance in picturing the disease in childhood if the statistics of the most important symptoms found in 500 consecutive cases are given. These symptoms were recorded at the first visit and expressed the first view obtained by an out-patient physician; 248 complained of arthritic pains; 350 had heart disease; 245 had chorea; 137 had throat trouble; 39 had nodules.

Cardiovascular System.—It is the frequent implication of the heart which makes this one of the most formidable diseases in temperate climates; and the study of the heart affections in one of much practical importance. Experimental evidence has shown that a diplococcus which is present in human cardiac tissues damaged by rheumatic fever can produce endocarditis, pericarditis, and fatty degeneration of the myocardium with dilatation of the heart and formation of submiliary nodules both in rabbits and monkeys. These animals may sometimes recover from this acute endocarditis and a healing lesion be found later.

The chief cardiac lesions in man are (1) acute dilatation of the heart, (2) endocarditis, and (3) pericarditis. In almost all the severe cases, however, the damage is a complex one; that is to say, the endocardium, myocardium, and pericardium are affected, and to this condition the term "carditis" is often applied.

There are very considerable differences in the development of these lesions. Sometimes the attack is rapid and severe, and in a short time the heart is terribly injured; in others there is an insidious onset and a gradual downhill progress; while in others the damage is as fleeting as that to the joints. It is accordingly most essential to recognize the earliest warning of heart disease, in order that the patient may be at once placed under strict treatment. This warning is, as a rule, acute dilatation of the heart, the importance of which has long been insisted on by D. B. Lees. The evidences of it are the following: (1) A slight rise in the frequency of the pulse rate. (2) The cardiac impulse becomes diffuse and extends beyond the vertical nipple line. (3) The area of deep or relative cardiac dulness is increased to the left, and sometimes to the right and upward. (4) The first sound at the apex becomes short, and the second sound in the pulmonary area is accentuated. (5) A soft systolic murmur can not infrequently be detected internal to the left vertical nipple line. These are the earliest signs of rheumatic heart disease, and this dilatation may entirely disappear

The rapidity with which dilatation may occur is most remarkable, and this is true both of the adult and the child. The explanation, however, is not easy unless it be associated with some sudden damage to the cardiac nerves and loss of muscular tone. The patient shows but few signs of cardiac dilatation unless it is acute and severe. If he has not been confined to bed there is shortness of breath on exertion, with a sensation of faintness and weakness. When more severe there are muscular weakness, pallor, restlessness, and well-marked dyspnœa.

Allusion has been made to the production of myocardial disease in animals by experimental inoculations of the diplococcus; fatty changes in the cardiac muscle fibers are thus produced, with dilatation and antemortem thrombosis. These facts are interesting and important, for there are instances on record in which death has occurred in man from acute rheumatic dilatation of the heart. In these rare and fatal cases of acute dilatation the symptoms are most urgent. They are dyspnea, pallor, vomiting, and delirium; the pulse is rapid and feeble, and the heart irregular, with no palpable impulse. The sounds become almost inaudible, although a mitral murmur may be heard in the region of the left nipple. The end may be by sudden syncope. In passing, the writer would also emphasize a definite group of cases in which the dilatation of the heart remains more or less chronic and relapsing. These are intractable in their course, and the patient suffers much from an irritable action of the heart, from breathlessness and nervousness. A superficial observer may miss the dilatation, and, hearing no murmur, dismiss such a case as functional. They recall a condition met with after influenza and some cases of diphtheria.

Modern investigations with the polygraph and electrocardiograph, coupled with the discovery of the focal myocardial lesions, have led to a considerable literature upon disturbances of rhythm, due to invasion of the primitive bundle by the submiliary nodules. In the writer's experience those focal lesions in childhood take but a comparatively small part in the history of rheumatic heart disease, which is usually a much more complex lesion. It is in these primarily myocardial cases, however, that now and again striking examples of arrhythmia arise, and again in acute virulent carditis evidence of heart-block, more or less complete, may be forthcoming.

Endocarditis.—The valves on the left side suffer more than those on the right, although in childhood the tricuspid valve is not infrequently damaged to a small degree. The tendency for endocarditis to attack the left side is also seen in experimental endocarditis, and experiment further shows that the infection is by way of the coronary arteries. This tells against the view that the special involvement of the left side of the heart is due to the presence there of arterial blood. In childhood multiple valvular lesions are common.

Acute simple endocarditis gives rise to but few symptoms, and it frequently happens that a patient comes under observation with a valvular lesion of which he can give no clear history. On this account there are few more important rules in medicine than "in all cases of suspected rheumatism to examine the heart repeatedly." A rise in

temperature of a degree or more, accompanied with pain in the chest, palpitation, and breathlessness, are suggestive, and examination of the heart may show that the action is unduly rapid, and that there is some dilatation.

(*a*) *Mitral Endocarditis.*—The first result of this lesion is regurgitation, which shows itself by a soft systolic murmur audible at the apex and traceable toward the axilla. In some cases there is a prolongation of the first sound before the bruit appears, and another important physical sign is a persistent reduplication of the second sound at the apex, which points to a thickening of the mitral segments. Lastly, it is not unusual to hear in the child a to-and-fro murmur over the apex, which is of mitral and not aortic significance.

(*b*) *Aortic Endocarditis.*—The first result of this is aortic regurgitation. Experimental inoculations have caused aortic and mitral endocarditis in animals, and also aortic endocarditis without any other valvular lesion. In man, also, aortic endocarditis may occur as a solitary lesion, although it is more usually combined with the mitral lesion. The physical signs which direct attention to aortic disease are the following: (1) Cardiac excitement: (2) a loss of definition of the aortic second sound; (3) the appearance of a soft diastolic and sometimes also a transient systolic murmur. The aortic diastolic murmur is frequently heard more distinctly to the left of the sternum.

The combined aortic and mitral lesion is a very serious and not very rare occurrence in childhood. It is more common in the male than in the female. The writer would emphasize the importance of this combined lesion and the necessity for listening for the aortic diastolic bruit to the left of and over the sternum. The frequent combination of the two lesions suggests a direct spread of infection in some cases from one valve to the other, a result experimentally demonstrated by Paine and the writer.[1] These cases if severe are not only liable to be fatal at an early age, but also may develop a malignant form of rheumatic endocarditis in early adult life. Acute endocarditis, if it is severe, soon leaves its impress, and this is particularly the case with the aortic lesion in childhood. The anemia is well-marked, and the striking pallor and forcibly pulsating arteries tell their own tale.

On the other hand, although a slight mitral lesion cannot be detected from the aspect of the patient, when it is more severe there is soon noticed a congestion of the bloodvessels of the lips and cheek, which with the purplish tinge of the blood suggests the lesion before the heart is examined. In acute endocarditis, œdema, if present, is slight; but in children the face is sometimes puffy, and an appearance results like that of renal disease.

The subacute type of inflammation, which leads to much fibrosis and contraction, is well illustrated by mitral stenosis. This is more frequent in the female than in the male. So insidious is the onset that it may not attract attention. Nevertheless, a careful study proves that it is associated with continued subacute attacks. In prolonged cases of

[1] *Quarterly Journal of Medicine,* 1912, v, 483.

chorea which drag on for months, and frequently relapse, this stealthy process can often be traced, surely and slowly crippling the heart. The association of chorea with mitral stenosis deserves the closest attention, and in this country is very frequent and of particular interest, because both lesions are far more frequent in the female and suggest peculiarity of the tissues of this sex in their reaction to the infection. It is also well-recognized that there are cases of mitral stenosis of mysterious origin, some of which are probably not rheumatic; but the following analysis of 50 cases under personal observation demonstrates the importance of rheumatism in the production of this lesion; 36 were females, 14 males; 3 appeared to be congenital. In 14 cases in which the lesion appeared to be a pure stenosis, 7 gave histories of prolonged or repeated chorea; and 6 of prolonged rheumatism. In 33 with stenosis and regurgitation, 22 gave a history of repeated chorea, and 9 of prolonged rheumatism. Thus, of 50 cases, in only 6 was no history of rheumatism obtained. Some of the early indications of mitral stenosis are:

1. There may be the signs of a slight mitral regurgitation which disappear to be followed by a progressive abruptness of the first sound. Later this abrupt first sound is noticed in association with a rumbling murmur which is diastolic, middiastolic, or presytolic in time, an accentuated pulmonary second sound, and a presystolic thrill.

2. Without any signs of mitral regurgitation, a progressive stenosis, as described above, may develop.

3. Most commonly the signs of stenosis develop in the presence of a persisting mitral regurgitation.

The malignant type of rheumatic inflammation is, in the writer's opinion, illustrated by some cases of malignant endocarditis in patients who have suffered from rheumatic fever. General opinion holds that malignant endocarditis is essentially a different disease; but the evidence in favor of the view that *some* of these cases are rheumatic is very strong. In the first place all members of the micrococcal group to which the diplococcus belongs are capable of producing malignant endocarditis, and it is highly probable that this diplococcus, which so often attacks the heart, would also produce the same condition. Again, if the clinical histories of cases of malignant endocarditis are investigated a frequent antecedent is found to be rheumatic fever. Some cases, moreover, commence with an onset indistinguishable from this disease, and exhibit during their course manifestations of it; the likeness, in fact, may be so close that even to the end of life it may remain doubtful whether it is simple or malignant endocarditis from which the patient is suffering. The late Dr. Andrewes, Osler, and others have long pointed out that malignant endocarditis may directly follow rheumatic fever.

These are in themselves suggestive facts, although the view that a secondary infection has been grafted upon the rheumatic one can still be maintained for their explanation. When, however, we turn to accurate experiment there is much more definite evidence. Paine and the writer showed in 1902 that in some of these cases of malignant endocarditis, with a rheumatic history, the diplococcus can be obtained in pure culture, and can further produce in rabbits not only simple and malignant endo-

carditis, but every stage between them. Again, with the diplococcus isolated from simple endocarditis of rheumatic origin, it is possible to produce not only multiple rheumatic lesions but also malignant endocarditis. Lastly, a first inoculation may produce simple endocarditis and another six months later produce the malignant type in the same animal. Further, these experiments teach that the test of the malignancy of a case of endocarditis is not the fungation of the vegetations, but the activity of the diplococci in the valve. The vegetations may be minute but the malignancy great, and the vegetations may be exuberant and yet the case be subacute. Although often called arterial pyemia, suppuration in these forms of malignant endocarditis is rare both in men and animals, although white infarcts are commonly discovered in both. The virulence of the infection sufficiently explains the "septic" type of these cases. This condition is fortunately a rare one and doubtless requires secondary causes to aid in its production. Among such causes are previous damage of the valves by former attacks, constitutions debilitated by unhealthy surroundings, the puerperal state, and probably anemia. In a recent paper with Paine the writer has again investigated this point in a study of combined aortic and mitral disease of rheumatic origin, and has shown that every clinical gradation from the simple to malignant may occur.[1]

The malignant type of endocarditis is to be suspected when there is a persistent and irregular fever and the appearance of the patient suggests severe poisoning. In a considerable number of cases there is a history of previous attacks of cardiac rheumatism, and in some rigors occur, which may be repeated and yet no abscess formation result. One striking feature in the heart is the persistent excitement. The cardiac murmurs may be unusually loud, or vary in character. Anemia, sweating, diarrhœa, infarction, and purpura are also important symptoms of this type. Some of these cases run a very protracted course, extending over months; others prove rapidly fatal. In other cases the diagnosis between simple and malignant endocarditis may hang in the balance for weeks and then the disease may slowly subside leaving much damage. The malignant type is rare in childhood.

Pericarditis.—The most serious form of heart disease in rheumatism next to malignant endocarditis is pericarditis—not so much on account of its intrinsic harmfulness as on account of the severe type of infection which accompanies it, and the involvement of the myocardium. It is more frequent in childhood than in adult life. The most characteristic examples occur in the first week of the rheumatic attack; but there is no period in which it may not appear. There are three chief types:

1. Simple acute pericarditis; (2) chronic relapsing, adhesive pericarditis; (3). malignant pericarditis.

1. The early symptoms of acute pericarditis are a rise of temperature, precordial pain, and dyspnœa. The pulse is excited and the tension low. Pericardial friction is usually detected within twenty-four hours, at the base of the heart, and may rapidly become audible over the entire

[1] *Quarterly Journal of Medicine*, 1912, v, 463.

cardiac area. A more unusual symptom is delirium. The distress in the adult is great, and shows itself in the anxious face and orthopnœa; on the other hand, some children show curiously little discomfort. The great enlargement of precordial dulness, so frequent in pericarditis, is chiefly the result of dilatation, and not of a large effusion. Ill-omened symptoms are vomiting, restlessness, delirium, and lividity, with progressive signs of cardiac failure. A first attack is not as a rule fatal, but pericarditis is the most frequent cause of death in rheumatic fever.

2. The chronic adhesive type is frequently found in childhood. This form is subacute, but very intractable, and gives rise to complete and dense pericardial adhesions. It may be associated with mediastinitis, pleuritis, and sometimes also peritonitis; and it is probable that some of those remarkable cases named multiple serositis by American writers are the result of rheumatism of this type.

3. The malignant type is rare and best illustrated by the following account of a fatal case: C. D., aged seven years, had an attack of rheumatic fever when six and one-half years of age, from which he recovered. Three weeks before he came under observation he was attacked by pains in the elbows, shoulders, wrists, and fingers, followed a few days later by precordial pain and dyspnœa. His condition from the first was serious. There was advanced mitral disease, he was pale and thin, and there were numerous rheumatic nodules. His illness extended over three months, and throughout there was irregular fever, each day the temperature rising to 102° to 104° F., and until the last week it never reached normal. Throughout this time the heart was persistently excited, and the idea of pericarditis was repeatedly suggested, but no definite friction rub could be detected. Crops of nodules came out and the boy gradually sank and died. The necropsy showed a pericardium greatly thickened and generally adherent, partly with subrecent adhesions and partly with recent plastic exudation. The left pleura showed a recent pleurisy. The mitral valve showed thickening and a few recent vegetations, as did also the tricuspid; the other valves were normal.

In this case, as was shown by the extensive pericarditis and the great thickening of the pericardium, there had been a persistent and progressive pericarditis extending over probably the entire three months.

The Blood.—This is much impoverished, and extreme, even fatal, anemia may result. During the acute phase there is a rapid fall in the number of the red corpuscles, and this anemia may be very obstinate. A moderate leukocytosis is frequent, and there is, in exceptional cases, a marked increase. It is difficult and exceptional to demonstrate the diplococci in the blood, for they are localized in the various lesions. This can, however, be done when the disease is very severe and generalized, and they can also occasionally be detected in the polymorphonuclear leukocytes. Lastly in severe cases there may be great hemolysis.

The Arteries, Capillaries, and Veins.—Legroux has recorded acute arteritis, the inflammatory changes commencing in the intima immediately beneath the lining endothelium. Barre has also recently

described an acute arteritis of the brachial artery attributed to rheumatic fever. In the subacute lesions, a perivascular fibrosis occurs which must, by contracting the lumen of the minite arterioles and capillaries, interfere with the circulation of the affected part—synovial membrane, pericardium, etc.—and thus assist in contributing to the indolent nature of the lesions. It is an interesting speculation whether this process may not, when on an extensive scale, be a factor in arteriocapillary fibrosis.[1]

Phlebitis with venous thrombosis may be a result of the rheumatic infection. In 7 cases under the writer's observation this took place in the large tributaries of the superior vena cava. This complication is to be suspected when a localized œdema of a limb, or of the chest or face, appears somewhat suddenly. If with this there is tenderness along the course of the veins, dilatation of collateral vessels, and lastly the sensation of a thick cord in the position of the vessels, the diagnosis becomes assured. French observers, however, have stated that its occurrence is more frequent in the lower extremities.

Articular, Fascial, and Muscular Involvement.—Arthritis is the most striking evidence of rheumatic fever. It is a symptom which in adult life comes into such prominence that it has been looked upon as a disease in itself, and termed "acute articular rheumatism." The objection to this term is very evident. The arthritis is generally polyarticular, and the larger joints, knees, ankles, shoulder, and hips are those most frequently attacked. It may, however, be monarticular. No distinction can be drawn between arthritis deformans and rheumatic arthritis from the frequency with which the larger joints are attacked, for in childhood the small articulations of the hand and fingers are often the seat of rheumatic inflammation and the hands may closely resemble the appearance presented by the acute form of arthritis deformans. In some cases in childhood the great-toe joints may resemble those of a gouty man. The acute course of the inflammation and the implication of the tendons surrounding the joints render the arthritis extremely painful. There may be much or little exudation, or there may be great pain with no very definite signs of arthritis at all. The articulations are hot and tender, and there is often a red flush over them.

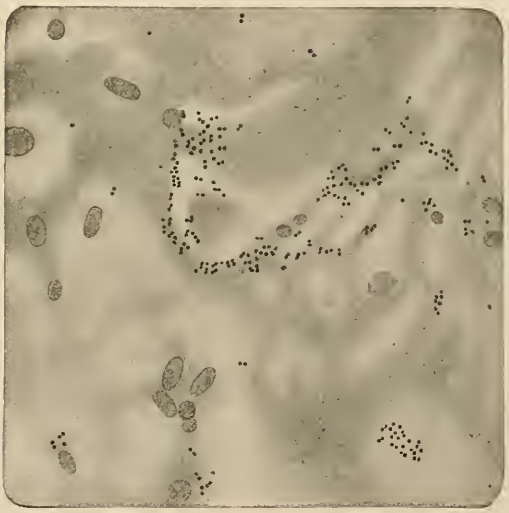
In animals arthritis is easily produced by intravenous inoculation of the diplococcus, and in them, too, the neighboring tendons are involved. Further, the stages of the process in animals can be studied in all its phases. There is at first a deposition of the micrococci in the subendothelial connective tissue of the synovial membrane, and, with this much capillary dilatation, even capillary hemorrhage. The endothelium is phagocytic, and numerous leukocytes pass into the subendothelial connective tissue, and by these means the micrococci are destroyed. The exudation, at first clear or blood-stained, later becomes fibrinous, and if the arthritis is very severe much of the endothelium is destroyed and many leukocytes and endothelial cells, together with diplococci, pass

[1] In a rabbit by intravenous inoculation, Paine and the writer have produced aortitis with calcification of the first part of the aorta. The lesion occurred in three weeks and there was also multiple arthritis.

into the synovial cavity. The capsular tissues also swell and become gelatinous in appearance. A local inoculation of the micrococcus into the knee-joint in a rabbit will, as Shaw pointed out, sometimes be a cause of endocarditis.

It is because rheumatic arthritis is often a simple synovitis, and probably because the diplococci are rapidly destroyed in the tissues, that it usually runs such a rapid course. A condition of osteoarthritis and also a chronic synovitis can be produced by the "diplococcus rheumaticus" in rabbits. Paine and the writer in 1910 showed two striking examples, one of which is now in the Hunterian Museum. Beattie and Yates have kindly allowed the writer to see an as yet unpublished investigation in which they have recorded not only relapsing arthritis and osteoarthritic changes, but have demonstrated the micrococcus in the synovial tissues of rabbits, at intervals extending from some weeks to twelve months after the onset of the arthritis. Further, they have demonstrated the micrococci in the synovial membranes after intravenous inoculations. These results strongly support the writer's contention that the infective agent may remain quiescent, but not destroyed, for long periods of time in the human tissues.

FIG. 42



The diplococcus rheumaticus in a rheumatic nodule.

The tendons are often damaged by an inflammation of their sheaths; gangliform swellings may appear, and as a sequel painful adhesions sometimes result. *The periosteum* also may be attacked and painful; fixed, periosteal nodes develop.

The most interesting and remarkable of the inflammations in the connective tissues are the *subcutaneous nodules*. These are the result of a local deposit of the diplococci in the subcutaneous tissues. The writer has shown with Paine a section in which the diplococci were

actually found in a minute bloodvessel in the tissue of a human nodule. The usual changes result, viz., swelling of the connective tissue, dilatation of the blood capillaries, exudation, and necrosis of the most damaged area. The microörganism is destroyed by the living cells. These nodules are not, as they are so often termed, fibrous nodules, but inflammatory exudations. When, however, the inflammation is chronic, some fibroid change may occur in the necrotic area. Nodules can be produced in rabbits by injection of the diplococcus. In size they vary from a pin's head to an almond, and are often better seen than felt, if the skin over them is gently stretched and the light is thrown obliquely. In rare cases the skin over them is reddened and they become adherent to it, and slightly tender; but it is interesting to notice how little discomfort these nodules usually cause, even when they are developing rapidly and in numbers. This manifestation is much more common in childhood and it is one which varies also in frequency with different outbreaks. The nodules should be looked for over the bony prominences and along tendons, as, for example, upon the bony processes around the elbow-joint, and edges of the patellæ, along the tendons of the extensors of the fingers and toes, over the parietal and occipital bones, around the ankle-joints, over the vertebral spines, along the crests of the ilia, and on the spines of the scapulæ. They may appear and disappear in three days, and cannot for this reason be essentially fibrous.

Their great clinical interest lies in their frequent association with severe cardiac rheumatism. This is not an invariable occurrence, for occasionally they are almost the only rheumatic symptom, but, as a general guide, the rule (which we owe to Cheadle) that rheumatic nodules are associated with severe heart disease is a valuable one. Their diagnostic value is also considerable, for although nodules are met with in arthritis deformans, gout, and erythema nodosum, these generally differ in their distribution or appearance. They must as a rule be searched for, although there are exceptional instances in which the parents or patient have made the discovery.

A condition upon which accurate knowledge is more difficult to obtain is that of inflammation of the muscles and their fasciæ. "Muscular rheumatism" may arise from different causes, and to ascertain in how many cases it is truly rheumatic is most difficult. Froriep described in muscular rheumatism the occurrence of localized swellings in the muscles. These swellings are localized connective-tissue inflammations which when chronic produce fibrous nodules or strands in the muscular tissue. These nodules or strands may hamper muscular action or press upon nerve fibers. In rheumatic fever, A. E. Garrod has noted the occurrence of a node of this kind in a child, and in one case the writer has seen a similar one in the left pectoralis major. It is probable that the stiff neck, pleurodynia, lumbago, and tender feet are the result of changes of a similar nature.

Manifestations in the Nervous System.—The disease frequently damages the nervous system, and in its most severe form is often called "cerebral rheumatism." It has been frequently observed that children of

rheumatic parentage are often highly nervous and prone to headaches, night terrors, and insomnia.

Chorea.—There is perhaps no more remarkable condition than chorea, and although its association with rheumatism has been noticed for more than two centuries, yet the complete explanation of its symptoms remains a most difficult problem, because of the rarity with which opportunities occur for investigating the condition after death. These facts, however, have been ascertained:

1. Chorea is associated very frequently with rheumatic fever.
2. The association is of such a close nature that chorea, when rheumatic, must be looked upon as a manifestation of that disease.
3. The more carefully the examinations of the brain are conducted after death the more frequently are some definite lesions found.
4. Investigators have isolated micrococci from the meninges, cerebrospinal fluid, and brain, in fatal chorea.

In 1899 Westphal, Wassermann, and Malkoff, from a fatal case of carditis and chorea, isolated a minute diplococcus which produced polyarthritis in a series of 80 rabbits. In 1900, Paine and the writer observed remarkable twitching movements in a rabbit as a result of an intravenous inoculation of a diplococcus obtained from a case of fatal rheumatism. This microörganism was similar to that described by Wassermann. Since that date similar movements in rabbits have been observed by Fritz-Meyer, of Berlin, and Beattie, of Edinburgh; in both cases they were results of inoculations of a similar microörganism.

It cannot, however, be pretended that chorea has been reproduced, for in chorea the involvement of the highest nervous centres stamps it as a human disease. Nevertheless it is an interesting fact that such movements should have been produced by these inoculations and that the microörganisms have been demonstrated by Paine and the writer in the pia mater and in the blood capillaries passing into the motor cortex of the animal's brain. Since that date, also, they have isolated the diplococcus immediately after death from the cerebrospinal fluid of three further cases of rheumatic chorea, and by cultures from one of them have produced in rabbits not only arthritis, but also endocarditis and pericarditis. Gordon Holmes and the writer have investigated three fatal cases of chorea, including one in pregnancy, and found these changes in the nerve cells: (1) Practically all the cortical cells were affected, being swollen and distended; their tigroid had partly disappeared and their nuclei stained more deeply than normal. (2) In some of the cells the nuclei were shrunken and deformed with the outline of the cell bodies indistinct. There were also small areas of cortical softening. Fraenzel has demonstrated submiliary nodules in the pia mater.

The explanation that naturally suggests itself is that the microörganisms gain a foothold in the meninges and brain and probably also in the spinal cord, where, partly by the poisons that are produced and partly by the local lesions, they give rise to the phenomena. Whether, as Triboulet (père) maintained, the peripheral nerves also suffer in chorea is uncertain. At the present time it seems inadvisable to claim all cases of chorea as rheumatic, for it is but reasonable to suppose that

other allied microörganisms may possibly in a lesser degree produce chorea. Upon this point more evidence is needed. The recent statistics of the writer upon the relation of chorea and rheumatism are as follows: Of 500 consecutive cases of rheumatic heart disease and chorea in childhood, 220 came for chorea. Of these, 122 had obvious organic heart disease; 38 had dilatation with rheumatic arthritis and pain; 10 followed immediately upon a sore throat; 20 gave a decided family history; 15 were attributed to fright and shock, two of them developing heart disease later; 15 gave no clue, two of them succumbing later to rheumatic heart disease.

Chorea is far more frequent in childhood than in adult life. It appears at any period in the course of an attack of rheumatism. The writer's youngest patient was aged two years and nine months; she began to show signs of mitral stenosis at three years.

"*Cerebral Rheumatism*" (*Gravis*).—The most severe form is associated with hyperpyrexia, and is, in England, usually termed rheumatic hyperpyrexia. These cases are fortunately rare. The Continental term "cerebral rheumatism" is preferable to that of rheumatic hyperpyrexia, for grave symptoms may arise without extreme fever; and, although the fever is a most important and valuable sign, the general symptoms are not entirely due to it, but are also a result of the profound toxemia.

The onset occurs as a rule in the third or fourth week of the active disease, although it may also supervene after the temperature has remained normal for more than a fortnight. Unfortunately there are no means of discovering in what cases this particular danger exists, and it may supervene so rapidly that the medical attendant is completely taken by surprise. Warning symptoms are headache, delirium, sleeplessness, and vomiting. In some cases there is cutaneous hyperesthesia; in others frequency of micturition. When the condition is more advanced the mental disturbances become more serious, semiconsciousness supervenes, with spasmodic twitchings and irregular breathing; the pupils are contracted and the eyes widely open; the pulse increases in rapidity and the face becomes livid. The temperature may rise gradually and then leap up to 108°, 109°, and 110° F., or it may rise abruptly from the normal to hyperpyrexia. In some cases the other rheumatic symptoms abate when this condition supervenes. Death occurs in over 50 per cent. of the cases which are not promptly treated, and is almost invariable if the temperature rises above 106° F. Many patients die even with prompt treatment. Cerebral rheumatism is not always of this exceedingly severe type, and cases occur in which dangerous symptoms, such as delirium, high but not extreme fever, and headache, are met with and then abate, and this may occur more than once in a single attack. It is exceptional to find any gross cerebral lesion after death.

Spinal Lesions.—There is much uncertainty about these lesions, and the question is complicated by the occurrence of arthritis as a result of nervous diseases. This makes it difficult to decide in doubtful cases whether the primary cause is a nervous one and the arthritis a symptom of it, or whether the nervous disorder and the arthritis are both results

of some general infection such as rheumatic fever. An interesting example of a probable rheumatic paraplegia is quoted by A. E. Garrod in his monograph on rheumatism. The patient, a case of Alexander Raynault's, was a man, aged twenty-four years, who has passed through repeated attacks of rheumatic fever. His illness commenced with loss of power in the legs and sphincters, and was looked upon as an acute diffuse myelitis. Recovery of power commenced to show itself in two days, and was followed by multiple arthritis, and this in turn by endocarditis, and lastly by pneumonia and pleurisy.

Peripheral Nerve Lesions.—The peripheral nerves also suffer, and there may result either a symmetrical peripheral neuritis or a local neuritis. This may give rise to well-marked sensory symptoms such as tingling, numbness, and partial anesthesia; or to rapid muscular atrophy and trophic changes. Severe neuralgia, not infrequently affecting the scalp, may also be a result, and in some of these cases fugitive syellings, apparently œdematous in nature, may be detected over the tender points.

Respiratory System.—The occurrence of tonsillitis has been remarked upon for many years. Striking examples occur which leave little room for doubt that the throat is one channel of infection. In 1900 Paine and the author isolated from a patient with tonsillitis a diplococcus which resembled in all respects the one they had already isolated from such rheumatic lesions as endocarditis, pericarditis, and arthritis, and it led to similar experimental results. These facts suggested the conclusion, long suspected, that invasion could be through that channel. It is clearly most hazardous to draw deductions as to the causation of rheumatic fever from cultures taken from the throat alone, but there is now practically a consensus of opinion that certain "streptococci" found in the throat are very liable to produce multiple arthritis and carditis on experimental intravenous inoculations in animals.

The usual appearance of the "sore throat" is a diffuse redness with some swelling of the tonsils and the palatal mucous membrane. Follicular tonsillitis is also met, and, less commonly, a condition closely resembling diphtheria, or that found in some cases of scarlet fever. The tonsillitis in rheumatic fever is often but slightly painful, and for that reason easily overlooked. In childhood it may occur as an isolated event in the prolonged history of a rheumatism, and may probably be then interpreted as a successful effort on the part of the tissues to destroy the invading microörganisms, either entirely at the local site, or to such an extent that those which enter into the system are unable to produce detectable visceral lesions. There is no relation between the severity of the sore throat and the gravity of the rheumatic attacks. Another point to which attention must be directed is that chronic enlargement of the tonsils with or without adenoids is very frequent in this disease. In such tonsils there may be deep foci, and the writer has seen such unhealthy areas concealed beneath the stump of an amputated tonsil when the remainder of the organ had been enucleated. Should an operation be done upon the tonsils in a state of active angina, an attack of rheumatic fever may follow, the first symptoms showing about the third day.

Enlargement of the cervical glands with tenderness is often associated with rheumatic angina.

Lungs and Pleura.—Pleurisy is a common occurrence, and can be experimentally produced in animals. It is met with in the majority of cases in which there is severe pericarditis, and adds greatly to the suffering of the patient. It is a serofibrinous inflammation which in the process of resolution is very liable to give rise to adhesions. These are frequently discovered between the pericardium and the adjacent surfaces of the pleura in fatal pericarditis, and the physical signs of pleurisy in that situation are characteristic. In addition to pain in the chest, there is pleuropericardial friction. Pleuropericarditis is a painful complication of pericarditis. Should it occur alone it must not be mistaken for pericarditis itself, for the prognosis is far less grave in pleuropericarditis, where the outer surface only of the parietal pericardium is damaged, than in pericarditis, which is essentially a disease of the heart itself. In exceptional cases the effusion may be sufficient to require tapping and the diplococcus has been isolated.

Pleurisy may and frequently does occur without pericarditis, but how often as a solitary rheumatic manifestation is a disputed point. Nor does one see how an agreement can be arrived at, since rheumatic pleurisy tends to get well and seldom needs surgical measures. Nevertheless at the present time when the statement is so frequently made that simple pleurisies are tuberculous, this form needs to be taken into account. There is nothing peculiar in the symptoms.

Pneumonia occurs in the severe types of rheumatic fever, and also results in animals from experimental inoculation. It is usually a bronchopneumonia. The temperature rises rapidly, and an unusually high fever, apart from hyperpyrexia, should always suggest the possibility of pneumonia. This is a point of some practical importance, for there is a natural desire not to distress a patient by movement, and thus the occurrence of pneumonia may be overlooked. There may be a considerable area of collapse around the pneumonic patch, and this gives the impression of a condition more extensive than that which actually exists. The consolidation may clear up with great rapidity, although the temperature may remain elevated because of other manifestations.

Acute pulmonary œdema is very rare and in the three cases observed by the writer all were complicated with carditis. One recovered; two rapidly died. The necropsies showed an œdema comparable to that in nephritis, involving the upper lobes of the lungs more than the lower. The physical signs are characteristic, for, with great embarrassment of respiration fine crepitations appear. The kidneys do not show gross changes. There is a possibility that very large doses of salicylate of soda may predispose to this highly dangerous condition.

Bronchitis.—The evidence of a rheumatic bronchitis is not certain.

Laryngeal Affections.—Rheumatism of the crico-arytenoid joints, with some laryngitis, have been recorded by Hirsch and other writers.

Cutaneous Manifestations.—The eruption most commonly seen is a form of erythema—an erythema marginatum or an erythema papulatum. Erythema marginatum appears over the trunk and extremities in the

form of rings, which are sometimes mistaken for ringworm or erythema iris. The rings are pink, slightly raised, and encircle skin of a livid color. In size they vary considerably, and several may coalesce into large gyrate areas. There are but few symptoms accompanying this eruption, but there may be some local tingling and irritation. As the rash fades it leaves a stain, and if, as is sometimes the case, there have been hemorrhagic areas, these discolored patches last for a long time. In erythema papulatum the papules vary in size, are usually symmetrical, come out in crops (especially upon the dorsal surfaces of the extremities), and fade, leaving a stain. In color they are bluish pink. In both these eruptions there is often a hemorrhagic element. Bullous eruptions are also met with in which the bullæ contain a clear fluid as in pemphigus. Purpura is also seen during acute attacks. Small macules appear particularly over the lower extremities, and occasionally a curious irregular net-work is formed by interlacing lines of purpura. Sometimes the purpura is severe and accompanied by sanious bullæ.

A scarlatiniform eruption has been described. In one case under observation there was a general erythema of the scarlatinal type, but lacking in the punctiform character. There was no reason to believe that it was a case of scarlet fever, and there was no desquamation, although this would not disprove the rheumatic origin of the rash.

The relationship of erythema nodosum to rheumatic fever is still disputed. At the present time the position stands thus: Erythema nodosum appears to be frequent in the rheumatic, and in some instances to be associated with such active signs as endocarditis and arthritis. On the other hand, many cases of erythema nodosum run a course of their own, and appear to have no relationship with rheumatism, and for these reasons some observers believe it to be a special disease closely allied to, but not identical with, rheumatic fever. Others believe it to be rheumatic, while others again look upon it as symptomatic of various infections and among these the rheumatic. Further investigations are needed to decide these questions. Erythema nodosum may be general although rarely so, and with it there may be subcutaneous nodules over which the skin is not reddened, and which if cut into are proved to be the results of great vascular hyperemia and serous exudation.

These eruptions may be the first symptom of active rheumatism, or may appear during the course. As with other manifestations the frequency of cutaneous lesions differs in different epidemics.

Rarer Manifestations.—*In the Alimentary System.*—It has been frequently noticed that rheumatic children have a weak digestion and are liable to bilious attacks and mucous diarrhœa; but it is difficult to assign a part in their causation to active rheumatism, and it is doubtful whether the epigastric pain that rheumatic children so often mention is gastric in origin. Experimental investigations also show that a mucous diarrhœa is not uncommon in animals. In adults some cases of extreme difficulty arise in which there is acute gastric dilatation or distension of the colon, with almost unsupportable outbursts of pain. If with these there is associated carditis the condition is serious and the illness may be very prolonged or even fatal. Peritonitis is a more common occurrence, and in

fatal cases of rheumatic fever a chronic peritonitis may be found around the liver and spleen. On one occasion the writer heard loud peritoneal friction during life; and in another there was complaint of abdominal pain over the upper segment of the abdomen, and peritonitis was demonstrated, after death, in this position. It has also been produced experimentally, and, further, the micrococcus has been isolated from the exudation in man. Certain writers have maintained that there is an association between rheumatic fever and appendicitis. These have been seen during life, but the writer has never found acute changes in the appendix in a fatal case of rheumatic fever. The frequency of the two diseases raises the possibility of coincidence.[1] In 1911 Paine and the writer produced appendicitis in rabbits by the intravenous inoculation of the diplococcus from a case of rheumatic fever. The organisms invaded the appendix from the peritoneal surface.

Genito-urinary System.—Among the rarer incidents is the occurrence of acute nephritis, and experimental investigation has thrown considerable light upon this subject. The diplococcus is freely excreted in the urine of animals that have been injected intravenously, and can be isolated from the urine of patients suffering from acute rheumatic pericarditis. In rare instances, as observed by Paine and the writer, and Vernon Shaw, acute nephritis may also result from these inoculations. The former have observed it in rabbits and in a cat. The cat within three days of inoculation developed profuse hematuria from which it eventually made a perfect recovery; during this period the urine swarmed with diplococci. After recovery the animal was killed and no trace of endocarditis was discovered, which excluded the possibility of a gross infarct.

Acute nephritis has also been recorded in man by various writers, among them George Johnson, Leyden, Dickinson, Hayem, Lees, and Garrod. The author has met with several instances in childhood. Another point of interest is the occurrence in man of large white kidneys in some cases of malignant endocarditis, and of nephritis with continuous hematuria in others, to which special attention has been drawn by Litten. A condition of large white kidney has also been produced by experimental inoculation of the diplococcus into rabbits, occurring with malignant endocarditis.

A far more difficult question is the possible influence of rheumatism in causing chronic renal disease. Leyden has directed attention to the fact that although acute rheumatic nephritis as a rule clears up rapidly, there are cases in which it drifts into a chronic nephritis. Can rheumatism, in addition to this, produce a change in the kidney, one which is never acute, but which terminates in a granular condition? It must be admitted that very many acute cases show no changes in the urine so far as albumin and blood are concerned; yet, on the other hand, in acute arthritic rheumatism, and even in chorea, albuminuria is not very rare, especially when the patient has not had sufficient rest. This albuminuria rapidly disappears, but may occur again on exertion and resemble in its behavior orthostatic albuminuria.

[1] *Proc. Roy. Soc. Med.*, Path. Sec., 1911, v, 19.

It is conceivable that in such cases there may be insidious damage to the kidney which slowly increases in a manner comparable to the slow contraction of the valve in mitral stenosis, and Beattie has observed experimental interstitial nephritis. This, too, is not altogether hypothetical, for a granular condition of the kidney is frequently met in necropsies upon mitral stenosis and is more frequent in women.

The Influence of Pregnancy and the Puerperium.—This has hardly received sufficient attention. As a general rule it may be stated that pregnancy and the puerperal state tend to produce a grave type. The severity of chorea in pregnancy is well recognized, and there is but little doubt that in a considerable number of such cases there has been a very definite history of rheumatic fever or chorea in earlier life. French and Hicks found in 29 consecutive cases a history of previous rheumatism in 19 and 15 of the 19 had suffered from chorea. The same intensification is sometimes noticeable with rheumatic carditis, which may become active and develop into the malignant type and prove rapidly fatal. In connection with this it is of interest that Paine and the writer observed that a rabbit which had recovered from rheumatic fever with endocarditis and arthritis died rapidly on reinfection, when pregnant, from malignant aortic endocarditis. The same type of endocarditis was also noted by Shaw under similar circumstances.

Mastitis.—Still has directed the writer's attention to the possibility of a rheumatic mastitis in childhood, and four patients have been under observation with active rheumatism and mastitis of the left breast.

Thyroiditis has been observed; and in chorea, there is sometimes complaint of pain in the thyroid gland, and, more rarely, some swelling and tenderness is observed.

Parotitis has also been recorded.

Lymphadenitis.—In all cases of fatal rheumatic pericarditis the mediastinal glands are considerably enlarged, and in some cases of tonsillitis associated with rheumatic fever the cervical glands are swollen. It is exceptional to meet with a general enlargement of the lymphatic glands.

Eye.—Conjunctivitis, erythematous and phlyctenular, is met with, and in rare cases acute iridocyclitis complicates an acute attack. This latter lesion is occasionally produced in rabbits by the intravenous inoculation of the diplococcus.

Diagnosis.—The diagnosis of the articular type and in an adult is a simple enough matter. The multiple and painful arthritis, the sweating, dilated heart, metastatic character of the articular lesions, and the reaction to salicylate of sodium, with rapid subsidence of the arthritis, all combine to make the disease a very characteristic one. It is, however, a very different matter when the disease is abarticular, the onset gradual, or the symptoms unusual; and although this division is in no sense a scientific one it will serve to make this part of the subject clearer if the diagnosis is first considered in the child and then in the adult.

1. **In Childhood.**—In many cases children with a rheumatic family history drift *gradually* into rheumatic fever. They are "out of sorts" for some weeks, with malaise, wasting, epistaxis, nervousness, slight fever, and fleeting pains. Such an occurrence should suggest the possibility

of an acute attack in the near future. Fever, multiple arthritis, and cardiac dilatation in a child usually mean rheumatic fever.

One serious mistake is to confuse *acute osteomyelitis* and rheumatic fever, for a life may be lost by procrastination. From the first, acute osteomyelitis is a serious condition. There may be shivering or actual rigors, the pain in the affected limb or limbs is very severe, and the region of the inflammation rapidly becomes swollen and sometimes brawny. Importance must be attached to the position of greatest tenderness—which is over the epiphysis and not in the joint—to the high fever, prostration, and delirium. The best safeguard against error is the knowledge of its possibility.

A more difficult problem is sometimes offered by *acute anterior poliomyelitis*, for in the early phase of this disease there is often a good deal of pain and fever. A loss of reflex, if it occurs, is a valuable aid, as also marked wasting. It is the early stage that there may be great doubt and an opinion may need to be given with caution. There is no swelling of the joints or heart disease in anterior poliomyelitis.

A mistake that is made more often perhaps than would be expected is that of confusing *infantile scurvy*, which is not uncommon under two years of age when rheumatic fever is exceedingly rare. In a doubtful case at this age scurvy should always come first into the mind of the practitioner. The gums must be examined for ecchymoses, the bones for periosteal swellings, and the skin for purpura. Hemorrhages from the kidneys or from mucous surfaces, pallor of the face, and extreme tenderness, are suggestive of scurvy. The heart is not damaged, and, when once this condition is remembered, the diet and the result of its alteration will soon solve any doubt.

Congenital Syphilis.—There are two conditions in congenital syphilis which may give rise to confusion. The first is the comparatively uncommon pseudoparalysis. In some instances this is accompanied by epiphyseal swellings; in others no swelling can be detected. Here again it is the pain which gives rise to the error. An inquiry into the history, the complexion of the child, its age, and the presence of the well-known stigmas of congenital syphilis, will prevent this error. The fact that the swelling is epiphyseal and not articular is also important. The second condition is met with in older children, and is a syphilitic arthritis. There are different forms of this, and although many joints may be damaged the knees are the most frequently attacked. The course is slow and the condition not very painful. It is a lesion which is associated with keratitis, peg teeth, and syphilitic deafness. The heart is usually spared, and there is no history of a previous attack of rheumatic fever. The Wassermann reaction is of additional assistance.

Gonococcal arthritis, if due to infection from the mother, shows itself in the first five weeks of life, and is usually associated with ophthalmia. It is uninfluenced by treatment with salicylates. Gonococci may be demonstrated in the exudation.

It may seem almost fanciful to mention *appendicitis* as a possible cause of confusion, yet in childhood this difficulty may arise. The particular cases are those in which rheumatic fever affects only one

joint, and that the right hip. In such cases children are apt to refer the pain above Poupart's ligament over the region of the appendix. These cases are unusual, and as a rule other joints are soon affected or other rheumatic manifestations appear.

Acute Tuberculous Arthritis.—Clinically, this arthritis is indistinguishable from the rheumatic, but proof has been furnished in a certain number of cases by the demonstration of tubercle bacilli in the joints. As a rule the differential diagnosis turns upon the presence of active tuberculosis elsewhere and the absence of any history of rheumatic fever.

There is a curious group of cases of multiple arthritis which has been carefully described by Still. This form commences usually in an insidious manner before the second dentition, although in exceptional cases the onset is acute. There is a progressive enlargement of the joints, mainly periarticular and the effusion as a rule is inconsiderable. The muscles waste and contractures are not uncommon. One feature is an enlargement of the lymphatic glands, which bears a distinct relation to the affected joints; and another is enlargement of the spleen, which occurs with considerable frequency. Anemia and sweating with pyrexia are further symptoms, and although heart disease is exceptional, adherent pericardium has been found; and in other cases endocarditis has been detected. It would be premature to attempt to explain their nature, but it is certain that they are not all tuberculous.

Arthritis Deformans.—Arthritis deformans is rare in childhood. Some writers consider the arthritis just described as a form of this; but, in addition, cases occur in which there are lipping and bony outgrowths, and in which the muscular wasting is extreme, and yet the heart escapes. Arthritis may occasionally be a prominent symptom in posterior basic meningitis. The results of lumbar puncture may give the diagnosis.

2. **In adults.**—*Arthritis deformans* and *gout* sometimes cause difficulty. In arthritis deformans the marked implication of the smaller joints, the course, the failure of salicylate treatment, the muscular wasting, and the rapid action of the heart (which is generally free from organic disease), are some of the main points relied upon for diagnosis.

Gout.—The differential diagnosis between rheumatic fever and acute gout is generally easy. Gout is more usual over thirty. The frequent implication of the great-toe joint and frequent escape of the larger joints, the occurrence of tophi, and the absence of heart disease, are striking differences. The habits of the patients are also suggestive.

Gonococcal arthritis may lead to error. The history of urethritis is a cardinal point. The arthritis is stubborn, the plantar fasciæ are frequently implicated, and iritis is more frequent. The heart is less liable to suffer, and the salicylates have but little influence.

In adults and in children *influenza* may cause difficulty. The severe pains and dilatation of the heart in themselves are liable to cause confusion, and the frequent occurrence of a sore throat adds to the similarity. Arthritis also is not very uncommon as a result of influenza. In the majority of cases the onset is more abrupt than that of rheumatic fever, and when the onset of the latter is more acute than usual the multiple

arthritis develops rapidly. On the other hand, the arthritis of influenza is usually a late result.

Pyemia with suppurative arthritis, both in adults and childhood, may be most difficult to distinguish especially in some cases that follow acute otitis media. The comparative rarity, however, compared with the frequency of rheumatic fever is important. The prostration and general poisoning are more profound in pyemic arthritis. Foci may form in the subcutaneous lesions and break down into small abscesses. Rigors and a high fluctuating temperature are further warnings. The heart becomes rapid and feeble, and although endocarditis is not so frequent, suppurative pericarditis may supervene most insidiously without the appearance of any pericardial friction.

Pneumococcal arthritis is usually sufficiently severe to demand an investigation of the fluid, and from this the pneumococcus may be located; although perfect recovery may occur, the type is more septic. and usually only one or two joints are affected.

Malta fever differs in the occurrence of sudden outbursts of pyrexia with severe prostration, alternating with intervals of comparative health. The *micrococcus melitensis* gives a definite serum reaction (Wright).

Acute rheumatic arthritis in one joint may be mistaken for a sprain. This is a not very uncommon error, sometimes upheld in spite of the appearance of a "sprain" in the other ankle.

Hemophilic Arthritis.—The sudden hemorrhages into the joints must be distinguished by their abrupt onset and the family history.

Prognosis.—This is a complicated matter, and often the attempt at prophesy is a failure, or at the best suggestive of the Delphic oracle. It is concerned with estimating the danger to life in a particular attack, the general outlook for the future, and the liability to recurrence.

1. The danger to life in a first attack is not great. Hyperpyrexia is generally accepted as the most dangerous complication, and it is not possible, if this supervenes, to foretell what will be the issue. Acute carditis may prove fatal in a first attack, and its occurrence in a young and delicate child points to caution in the prognosis.

2. In judging of the outlook for the future, the *age* stands first. In general, the younger the patient the greater liability there is to further attacks, and to cardiac complications. The surroundings are also important; the child of poor parents who is living in an unsuitable climate and is badly fed and clothed is heavily handicapped. The nature of the attack is another consideration. The insidious form in the young, in which one manifestation appears after another, with the illness lasting for weeks and months, is most unfavorable. Carditis under six years of age with rare exceptions means the ruin of a life. Combined valvular lesions in childhood are also very serious.

3. In calculating the chance of another attack the age is important, for the younger the patient the greater the liability. A strong family history of rheumatism points to an increased liability, and if the circumstances or occupations are unsuitable the danger of more than one attack occurring is enhanced. The physician will often find it difficult

to say whether the symptoms are the result of a new infection or are the result of a fresh outbreak of a slumbering first infection.

Treatment.—This, although in some respect encouraging, is on the whole unsatisfactory. The disease may respond to treatment in a way which is almost magical; but cardiac complications in childhood are the despair of the physician. The subject divides itself into three parts: (1) The preventive treatment. (2) The treatment of the disease itself. (3) The management of those with an inherited tendency.

Prophylactic Treatment.—The disease must be prevented as far as possible, yet the prophylaxis seems hardly to have appealed to the medical profession sufficiently. The resigned acceptance of the fact that hundreds of young lives are damaged by rheumatism contrasts vividly with the extraordinary efforts that are made to prevent tuberculosis. All teachers should be acquainted with the early signs of chorea. School-rooms should be well ventilated, and every effort should be made to prevent children sitting in damp clothes and shoes.

Whatever views may be taken upon the general question of the relation of damp to rheumatic fever, there is good clinical evidence to prove that a rheumatic patient living in a damp house will drift from bad to worse. Epidemic outbreaks and the vagaries of climate are beyond our control; but much can be done by judicious advice to put parents or patients upon their guard against the danger during the changeable seasons. Simple rules warning the parents of rheumatic children of the dangers of the disease and the necessary care they require are helpful. Great attention should be directed to the care of the throat, the teeth, the nasopharynx and nasal passages. With chronic tonsillar disease the advisability of complete removal should be considered.

Management of the Acute Attack.—If possible a bed should be chosen of sufficient breadth to be comfortable to the patient, but sufficiently narrow to make it possible to manage him with ease. For the same reason it should be of a convenient height. The sick-room should be airy, but care should be taken to protect the patient from drafts. If there is profuse sweating the patient should be between soft blankets, but unless this is the case it is much more soothing to be between sheets, in a light flannel nightdress. The perspiration should be sponged off with a warm sponge, and the patient dried with a soft towel. It may be necessary to keep the bedclothes from the tender joints by a cradle.

While the disease is acute the diet should be fluid and mainly non-nitrogenous, for there are good reasons for believing that the renal functions are impaired. In the subacute type with carditis in children it is frequently advisable to allow as nourishing a diet as can be taken. Thirst can be quenched with lemonade, barley-water, or plain water.

Medicinal Treatment.—At the commencement of the attack the bowels should be opened. Calomel in a dose of 2 grains (0.13 gm.) followed by a saline generally answers admirably. Severe purging is unnecessary, and if the bowels are obstinate throughout the attack cascara or senna is suitable. *Alcohol* is not as a rule required, unless for some special crisis such as acute cardiac failure or hyperpyrexia. It is, however, useful in asthenic cases in which the tongue is dry and the prostration

considerable. If the throat is affected a chlorate of potash and salicylate gargle should be employed if feasible.

Local applications to the joints are often of service. Warm cotton wool in most cases answers all purposes, with oil of wintergreen, belladonna, and opium liniment, or warm alkaline lotions. In some cases the pain in one joint may be exceedingly severe and persistent, and it is then advisable to fix it with a splint.

Of internal remedies the salts of salicylic acid first require consideration. Some maintain that these are true specifics, and go so far as to consider that symptoms which do not yield to them are not rheumatic in nature. If this view is a correct one these drugs are indicated in all forms of rheumatic fever, whether articular, cardiac, pulmonary, or nervous. Experience, however, has amply shown that their effect upon cardiac rheumatism is very feeble as compared with their effect upon articular rheumatism, and in explanation of this two reasons are advanced —that the drugs are not sufficiently pushed, and that the patients come under treatment at too late a stage. Unfortunately the fundamental statement that the salicylates are a specific remedy is not established; and a further question arises: Can they be pushed without detriment to the patient? It is clear that if the reason for their employment is not an absolutely sound one it would be unwise to push them if they are in themselves deleterious.

In the writer's judgment large doses of sodium salicylate are often detrimental, and in cardiac rheumatism, especially, may introduce new dangers and in critical cases may turn the scale against the patient. It is a difficult question, on the other hand, to decide whether these drugs prevent cardiac complications. This can be asserted, that rheumatic manifestations—for example the nodules—may appear even when large doses are being given; and also that in spite of the widespread use of the salicylates, cardiac complications are very frequent.

The ill effects of large doses of these drugs are general depression, a small pulse which is sometimes irregular or slow, vomiting which may be most difficult to arrest, deafness, dizziness, buzzing in the ears, delirium, and occasionally irritation of the kidneys. The gravest and most remarkable of all are respiratory disturbances. In some cases dyspnœa supervenes, with breathing like that seen in diabetic coma and the patient may collapse and die within twelve hours. These dangerous symptoms or severe vomiting may appear after a few large doses—*e. g.*, 20 grains—to a child of eight years. There is no doubt that sodium salicylate is, in large and continuous doses, essentially a depressant. In writing thus, the reader will clearly understand that the opinion expressed here is neither original nor by any means universally accepted. It is worth considering whether the depression of temperature produced by these drugs may not sometimes mislead us into a sense of false security.

The treatment of the articular form of rheumatism is much more encouraging, and in very many cases the salts of salicylic acid answer admirably. The treatment is more easily borne if the bowels are first opened by an aperient; and the particular manner in which the drug is administered will vary with the character of the case. If the patient

is a strong adult, 20 grains (1.3 gm.) of salicylate of soda can be given in combination with 20 grains of bicarbonate of soda and 20 minims of tincture of ginger, in 1 ounce of chloroform water every three hours, for four doses, then every four hours, later every six hours, and lastly three times a day. When there is much distress and insomnia it is advisable to give a sedative in the evening. A patient with a feeble circulation will bear the treatment better if the aromatic spirit of ammonia is combined in 15 to 20 minim (1 cc.) doses, or 5 minim doses of tincture of nux vomica, and if some brandy is given occasionally. Salicin is advisable for the delicate, and especially for delicate children.

When the temperature has fallen it is advisable to persist with salicylates in diminishing doses for at least a fortnight, rather than to leave them off abruptly. This is a general rule; the physician, however, will be guided by warning pains and by the temperature chart during this stage. A useful combination, after the disease is controlled, is salicylate of quinine; and from this during convalescence a change can be made to quinine, which can be prescribed for the adult in an effervescing solution.

A considerable number of different preparations of the salicylate compounds are now in the market. Among the better known are aspirin or salicyl-acetic acid, saloquinine-salicylate, and salophen (acetylparaamido-phenyl-salicylic ester). It is claimed for aspirin that it is pleasant to take, not a cardiac depressant, and not liable to cause gastric disturbances. It is certainly well tolerated, both by adults and children, but vomiting and depression will occasionally result from large doses. In adults it is prescribed in dose of grs. x. to xv (0.65-1 gm.). Some prefer to prescribe this drug both for adults and children in water acidulated with lemon-juice. Salophen, which contains over 50 per cent. of salicylic acid, is also prescribed in doses of from 10 to 30 grains.

The alkaline treatment has been superseded by the use of salicylates, although some physicians still find good from full doses of potassium citrate with potassium bicarbonate.

If the heart is not damaged and the course of the illness has been favorable the patient may be convalescent in three weeks. Relapses or recrudescences are, however, frequent, and a too liberal diet or too early return to active movement is generally blamed for them. It is, however, doubtful if a careful increase in the diet can be responsible for their recurrence. Active movement is more probably a factor, for there appears to be a decided tendency for all rheumatic manifestations to gain ground if adequate rest is not given.

It is a useful precaution to have the joints and limbs that have been attacked, massaged and exercised by passive movements before voluntary movements of any considerable extent are undertaken. At this stage a stimulating liniment is also helpful. In convalescence hydropathic treatment is of much service, but it is doubtful whether there is any remarkable virtue in the waters in the locality, but the systematic stimulation of the joints is most valuable when the disease is dying down and yet recovery is slow.

The inflammation may persist in one or two of the joints. Salicylates have no influence over this condition, and the erroneous diagnosis of a

gonorrheal arthritis is sometimes made on this account. If the joint is opened, clear or blood-stained fluid exudes from the connective tissues and cavity. In the acute stage the joint should be fixed by a splint, and a plaster of Paris case is very useful if it is made in such a way that it can be easily removed. A generous diet and plenty of fresh air are valuable adjuncts to the treatment of this troublesome complication. An occasional blister relieves the pain and sometimes does a great deal of good to the joint. As soon as light massage can be tolerated it should be employed, and later combined with gentle passive movements. Douching and skilled massage are invaluable when the patient can bear the treatment.

In other cases one joint remains obstinately distended with fluid, and here again good food, fresh air, and quinine are more successful than the salicylates. Blisters are often very useful in promoting absorption. If in spite of prolonged rest and counter-irritation the joint remains distended then skilful strapping with Scott's dressing (ung. hydrargyri co.) is indicated. The strapping should be tightened from time to time, and the joint kept at complete rest. If this fails, aspiration and flushing with 1 per cent. carbolic acid solution is valuable; after this the joint should be carefully and firmly bandaged, and if there is any suspicion of active rheumatism full doses of salicylate of soda should be given during the next few days. Bier's method of producing passive congestion has been much praised by some in the treatment of the more obstinate cases of arthritis, but the results vary.

Dry heat in the form of the radiant heat baths has been strongly recommended and is a valuable stimulant. There are no certain indications for its use, and it may fail in the thoroughly bad cases.

Iodide of potassium (gr. v, gm. 0.3) with salicylate of soda (gr. xv, gm. 1) often relieves the articular pains, which are worse at night. This nocturnal suffering is most distressing to the patient, and for this reason the above combination is always well worthy of trial.

The tonic treatment of the convalescent needs some care. The anemia that so often results requires iron. Arsenic is also useful, and may be given as Fowler's solution combined with alkalies, and the ammoniated tincture of quinine. For children cod-liver oil is often very useful, especially when they are thin. A dry inland climate is best for those of vigorous constitution. The feeble, delicate, rheumatic convalescent does better in a dry and mild climate.

Serum Therapy.—The idea of treating rheumatic fever with some curative serum is one that suggests itself. The antistreptococcic sera in use are antibacterial, very uncertain, and cannot as yet be standardized. Those, however, who believe that the disease is an outcome of a streptococcal infection have hopes that a polyvalent serum may do good. In our present ignorance of these most complex poisons and antidotes who can deny this? The believer in the specific character of rheumatism also cannot deny that other microörganisms allied to that found in the disease may possibly form in some degree allied or similar poisons, and must admit that such a serum may possibly do good.

The writer had no success with such a serum in six carefully chosen

cases, but Menzer has reported some successes with a serum manufactured by Merck. Menzer's serum produces very definite effects in subacute cases. After four to six hours, redness, swelling, and heat occur in the affected joints but in no others. For a time the cardiac symptoms also appear to be augmented, there are fever and pains in the neck and head, swelling of the lymphatic glands, and sore throat. Later there is a fall of the temperature by degrees, and then cure. The dose must be gauged by cautious use, the test dose being 5 to 10 cc. As much as 200 cc. have been used for a single case. Up to the present discordant results have been obtained with this serum, and the local reactions are somewhat disturbing.

Vaccine Therapy.—If the etiology put forward here is correct, this would appear to have a decided place. Unfortunately it is difficult to obtain accurate data, particularly at the present time when these methods appear to have partially mesmerized medical reason. It would seem to be especially indicated in the lingering cases in childhood when the temperature remains elevated and subacute lesions are persistently active. In some of these good appears to have followed; in other complete failure. Caution is very needful when there are active cardiac lesions, and with our present knowledge an initial dose of 1,000,000 would be the safest.

The treatment of rheumatic heart disease is too extensive a subject to be dealt with in this article, but a few points will be touched upon. The pain of pericarditis is much relieved by an ice-bag applied to the precordium. Continuous application is the most satisfactory. Unless there is painful arthritis the writer trusts to quinine, strychnine, opium, digitalis, and stimulants, rather than to the salicylates. In exceptional cases when the right heart is acutely dilated venesection is called for. Rheumatic pericarditis may be overtreated, and the patient be more harassed by measures for his relief than by the disease itself. Paracentesis should not be attempted until there is very definite proof that the symptoms are not from acute dilatation of the heart.

Rest in all forms of rheumatic heart disease is of first importance, and the guides for relinquishing it will be the rate of the pulse, the size of the heart, and the absence of breathlessness upon the resumption of active movement. Passive movements and massage are valuable introductions to more strenuous exertion.

"Cerebral rheumatism" with hyperpyrexia requires prompt treatment with hydrotherapy. The cerebral symptoms are even a better guide than the temperature for its employment. A temperature of 105° F. is a signal of danger. A temperature of 104° with headache and vomiting is of equal significance if there are no local lesions to account for it. The bath should be given at a temperature of about 85° F. and rapidly cooled. The patient is watched throughout with the utmost care, and the duration of the bath graduated by his strength and by the effect upon the temperature. If there is collapse he must be at once removed, rapidly dried, and wrapped in warm blankets. If his temperature falls in the bath—from 107° to 102° F., for example—the patient should be removed, for the temperature will fall to normal after

leaving the bath. Stimulants are needed and should be close at hand, but depressant antipyretic drugs are not advisable. The bath may need repetition several times in a severe case. If a bath cannot be given, ice sponging and cold packs may save life.

The Management of Those Predisposed to Rheumatism.—Careful attention should be paid to the warnings of rheumatism in children of rheumatic parentage, and the throat should be promptly treated if there is a tendency to tonsillitis. Among the wealthier classes the possibility of an unsuitable house or climate should be carefully considered. Such children should not be pressed at school work, and evening study often does them harm. When they are thin and irritable, enforced rest in the middle of the day is advisable. Woollen or wool and silk garments should be worn next to the skin, and if an acute attack has occurred and the climate is cold and inclement, it is advisable to winter in a dry and bracing atmosphere.

CHAPTER XXXII

FEBRICULA—GLANDULAR FEVER—INFECTIOUS JAUNDICE —MILIARY FEVER—ROCKY MOUNTAIN SPOTTED FEVER —PSITTACOSIS — FOOT-AND-MOUTH DISEASE — MILK SICKNESS—RAT-BITE DISEASE

By THOMAS R. BOGGS, M.D.

FEBRICULA

Synonyms.—Ephemeral Fever; Febris Herpetica; Leichteserkältungsfieber; Simple Continued Fever; Ardent Fever.

Definition.—Under the above is included a group of acute fevers characterized by a brief course of from one to several days and the absence of the diagnostic features of the specific infectious group. With the steadily increasing refinement of diagnostic methods and consequent sharper definition of diseases on an etiological basis this indefinite group has undergone a constant and gradual contraction. The older writers devoted much space to its consideration under such names as synochus simplex, febris sanguinea, febris continua simplex and the like, including in it many cases of mild atypical typhus and typhoid fevers and others which we are no longer able to recognize. It was only in the nineteenth century that this group was reduced to something like its present proportions. When all allowance has been made for errors in diagnosis and aberration from type in specific fevers, there yet remains a number of cases which must be classified under one or another of the above titles.

Etiology.—The causative factors are varied and indefinite. It is, in fact, our ignorance of the relation of specific microörganisms or toxins to these cases which compels us to accept such a classification as the above. In general it may be said that the young are particularly affected, the great majority of cases falling in the first two decades. The changeable seasons of the year show the greatest number of cases, while sudden exposure to great heat or excessive cold is frequently the determining factor. Vigorous persons of full habit more often suffer than those less robust.

Individual susceptibility plays undoubtedly an important role. There are many persons whose heat-regulating mechanism seems particularly unstable and in whom slight dietary indiscretions, emotional and intellectual excitement, or bodily fatigue, may be followed by a marked rise in temperature of greater or less duration, and, so far as we can determine, entirely unassociated with any localized infection or inflammation. It is this class perhaps which furnishes the best examples of

the ephemeral fever in the stricter sense, that is, of only twenty-four to thirty-six hours' duration.

Abortive types of the acute infectious disorders are often necessarily classed as febricula in the absence of the characteristic features. Such cases are particularly frequent after epidemics of diphtheria, scarlet fever, typhoid, or measles. Here we have only the prodromata with fever of a few days' duration and rapid convalescence. In this subgroup also, in all probability, belong most of the cases of febris herpetica described by Continental writers as occurring sporadically and in epidemics and distinguished from other cases of febricula by the frequent or constant appearance of herpes labialis during the fastigium or defervescence. The contention of some authorities that all cases of febris herpetica are abortive pneumonia lacks substantiating evidence. The proportion of these abortive specific disorders, formerly classed ephemera, has been greatly reduced in recent years.

Some authorities maintain that rheumatic fever may occur without any localizing manifestations and in a mild and abortive form. Central and abortive pneumonia in children unquestionably swells the list.

Gastro-intestinal disturbances account for perhaps the major part of the simple fevers. The absorption of toxins in the food, or those produced by fermentation or imperfect metabolism, is not infrequently accompanied by fever. This is especially common in childhood and, where the toxin is a recurrent factor, may give rise to a more prolonged continued fever. The stomach and intestines are normally very tolerant of partly decomposed food, and in most of these cases there must be some primary disturbance, reducing the bactericidial and digestive powers to a greater or less degree. The lumbricoid fever of French authors probably belongs in this class. Noxious vapors and sewer gas are held accountable for febrile paroxysms in certain instances. Just how these act is unknown, but clinically some very acute cases follow quickly on exposure to such influences.

Tropical heat is apparently responsible in a large measure for the incidence of ephemera, simple continued fever, and ardent fever in the warm countries. Those alien to the soil and unacclimatized are particularly affected, and we have all gradations of severity from mild fever of one or two days to the most severe and fatal heat prostrations. The reluctance with which many Europeans living in the East relinquish the habit of eating and drinking, of dressing and exercising just as at home, makes them especially open to attacks of this character. In a mild degree this type of fever is quite frequent in the winter resorts of the extreme south of Florida and the Bahamas.

Pathological Anatomy.—The autopsy findings may reveal some definite lesion, such as central pneumonia, typhoid ulcers, or general septicemia, and so enable us to determine the true nature of the affection. In other cases nothing more than general congestion of the viscera, with more or less œdema and exudation into the serous cavities, can be found. There is no specific anatomical picture associated with this group.

Symptoms.—Sudden onset with chilliness or definite rigor is very common, the temperature rising quite rapidly and reaching a moderate

or even high grade, 103° to 105°, in twenty-four hours. No definite incubation period is recognizable ordinarily, although in many instances it may coincide with that of some prevalent epidemic. The acute onset is especially characteristic of ephemeral fever, while simple continued fever is often preceded by a period of lassitude, loss of appetite, and slight headache, followed by a rather slower rise of temperature and a longer course. Accompanying the fever there is often some pain in the back and limbs, restlessness, insomnia, or drowsiness. The tongue is heavily furred, the urine scanty, and constipation is the rule, or less frequently a slight diarrhœa. In children the tendency to cerebral symptoms is more marked, delirium and even convulsions being not infrequent in the first twenty-four hours. The tonsils and pharynx are sometimes slightly inflamed and there may be a slight bronchial involvement. Fugitive erythema has been observed and sudamina over the chest, back, and abdomen. Labial and nasal herpes is frequent, appearing more commonly just before or during the defervescence. French and German writers separate these cases to form a group called febris herpetica, but the multiplication of terms is hardly justifiable.

The decline in ephemera is usually rapid on the second to the fourth day, and accompanied by profuse perspiration and critical discharges from the kidneys and bowels. Occasionally vomiting or epistaxis may occur at the crisis. In other cases the decline is slow and uneventful. In contrast to influenza there is commonly little if any residual depression or prostration. In the simple continued fever the course is from six to eight or even ten to fourteen days. The temperature is not so high and shows quite marked daily excursions. It may even be remittent or intermittent. The pulse is moderately rapid, full, and strong. There is some headache and more rarely delirium. The decline is often by lysis. Many of these cases are abortive typhoid and paratyphoid infections, such as the "Florida fever" of the Southern United States.

The "ardent fever" of the tropics is a severer form, occurring in newly arrived young persons. In it the cerebral symptoms are more marked, acute delirium being common, and may be followed by coma and death about the tenth day. The majority have a well-marked crisis and recover. It is quite certain, as pointed out by Manson and others, that many cases of so-called ardent fever are fulminant malarial infections in which the mild prodromal features have been overlooked.

Diagnosis.—At the onset and during the course of the disease we usually suspect something of a graver nature, and it is only after the entire course has been reviewed and all local and specific causes have been found wanting that we arrive at a diagnosis by exclusion.

Prognosis.—The prognosis in ephemeral and simple continued fever may be said to be uniformly good. A considerable mortality, however, is attributed to ardent fever in the tropics.

Treatment.—This is essentially symptomatic. Calomel and a saline may be indicated at the beginning, with cool or cold sponge baths when the temperature is high, and an ice-bag to the head in cases of headache, delirium, or epistaxis. The drinking of water should be encouraged,

and acidulated mixtures may be of benefit. Salol and phenacetine are useful when there is much pain. Restricted liquid diet is best suited to all types, with rest in bed until convalescence is established.

GLANDULAR FEVER

Synonyms.—Acute Cervical Adenitis; Drüsenfieber; Fièvre Ganglionnaire.

Definition.—A disease of children characterized by acute onset with fever, slight congestion of the tonsils and pharynx, accompanied by swelling, tenderness, and more rarely suppuration of the cervical lymph glands, especially of those lying behind the upper portion of the sternocleidomastoid muscle. Enlargement of the liver and spleen is common and acute nephritis sometimes occurs. Constipation is frequent, although diarrhœa may mark the onset. The disease is contagious and occurs most frequently in localized epidemics. The course is mild and complications are few.

The disease was first carefully described by E. Pfeiffer[1] in 1889, although cases had been noted and incompletely studied some years before. Park West[2] gives valuable statistics of the largest epidemic yet studied, with a report of 96 cases. In answer to critics Pfeiffer has reasserted his original claim for the validity of the symptom complex. In a recent review Schleissner[3] presents the arguments against the unity of the disease.

Etiology and Pathology.—Glandular fever is a disease of infancy and childhood, most of the cases occurring between the first and tenth years. Adults are rarely affected, although one or two garrison epidemics as well as isolated cases have been noted. The two sexes appear equally susceptible. Most of the cases occur in the late winter and early spring months and exposure doubtless plays some part as a determining factor. Many cases have followed other diseases, such as influenza, measles, and scarlatina, and it is probable that lowered resistance and malnutrition are contributory causes. In a large number of instances, however, there is no history of previous disease. Enlarged tonsils and adenoids have been frequently noted in association with glandular fever. Bacteriological reports are conflicting, and no specific causal organism has been established. That the disease is contagious is hardly to be doubted. House epidemics are common and there may be many local foci in one community. The frequency of slight inflammation of the tonsils or pharynx, with some pain on swallowing and the characteristic involvement of the glands which directly drain this area, point to this region as the portal of entry. The occurrence of cervical adenitis with some inflammation of the tonsils or pharynx, and occasionally severe nephritis, has suggested to some observers that the disease was abortive scarlatina or diphtheria. But so many of the cases have had one or both of the

[1] *Jahr. f. Kinderheilk*, 1889, Band xxix, p. 257.
[2] *Archives of Pediatrics*, 1896, xiii, 889.
[3] *Wiener klin. Woch.*, 1911, xxiv, 310.

diseases either before or after the attack of glandular fever that this hypothesis has little to recommend it. The incubation period is unsettled. In many cases it seemed to be from seven to ten days. The number of fatal cases is so small that there have been no thorough studies of the structural changes in the glands.

Symptoms.—The onset may be sudden, with fever, headache, loss of appetite, and constipation, or in other cases preceded by two or three days of fretfulness and general malaise. The temperature elevation is usually moderate, 101.5° to 103°, but may reach 104°. It is commonly remittent, being highest in the evening. The pulse and respiratory rates are proportionally increased. The tongue is furred and in most instances a slight reddening or injection of the tonsils and pharynx is found. Occasionally a very slight, filmy exudate is demonstrable on one or both tonsils. Nausea and vomiting sometimes mark the initial period and constipation is present in the majority of cases. Diarrhœa may occur and was considered by Pfeiffer as related to involvement of the abdominal lymph glands. Within twenty-four to forty-eight hours after the onset, as a rule, swelling of the glands under the sterno-mastoid muscle is evident, although this may be delayed until the fourth or fifth day. The glands increase rapidly in size and may be as large as an olive. They are discrete, commonly firm to touch, and very sensitive. The skin over them is normal, as a rule. Torticollis and pain on swallowing frequently accompany the swelling. Bilateral involvement is the rule, but unilateral involvement is also noted. In Pfeiffer's cases the swelling appeared first on one side and then involved the other, and the course has been similar in most other reports. Comby and Neumann, however, report unilateral swelling as characteristic of their cases.

As the glandular swelling reaches its maximum the fever declines by crisis, with occasional critical discharges from the bowels (Park West), or by lysis, while the swelling persists, disappearing slowly in the course of two to four weeks. In many instances there is a recrudescence with fever and general symptoms, with the involvement of fresh groups of glands, as axillary, inguinal, mediastinal, or mesenteric. Those first involved may also increase in size with the reinvasion. Other cases are described in which there have been several recurrences of the disease at intervals of weeks or months.

Enlargement of the spleen and liver is very common, although in some epidemics this feature is absent. The respiratory system is not affected, as a rule. Pain and tenderness in the umbilical region are associated with the involvement of the mesenteric glands in some cases. Erythema, urticarial eruptions, and herpes have been noted in a few instances. Suppuration is uncommon and yields readily to incision and drainage. Isolated instances of otitis media and parotitis have been recorded. Nephritis has been noted in a small percentage of the cases, and is the most important complication. It appears usually in the first few days of the disease and is of a hemorrhagic type. Most of the cases end in recovery; some become chronic and a few have been fatal. In case the nephritis begins late in the disease there is

a recrudescence of the cervical adenitis very like that associated with post-scarlatinal nephritis.

Diagnosis.—It is not until the characteristic glandular involvement has become evident that the disease may be recognized. Secondary adenitis from outspoken local causes should be rigidly excluded. Thus caries or abscesses of the teeth, thrush, follicular tonsillitis, pharyngitis otitis media, etc., may cause swelling of the glands. But in glandular fever the involvement is out of all proportion to the local signs and it is the particular group draining the tonsil which is especially involved, while in the other infections the distribution is apt to be irregular.

The slow development, persistence, and often painless character of tuberculous adenitis render it easy of recognition ordinarily. There is no doubt, however, that cases of glandular fever seen late after the febrile stage have been mistaken for tuberculosis. In such cases time and, where possible, tuberculin will clear up the difficulty. The torticollis and pain on moving the head, with very slight glandular swelling, easily overlooked, may lead to a diagnosis of meningitis at first. Where a rash is present the diagnosis may be very difficult if not impossible, until the course makes it evident from the appearance of the characteristic swellings. The early development of nephritis may cause suspicion of scarlatina. The adenitis of Hodgkin's disease, mumps, or syphilis should offer no serious difficulties.

Prognosis.—The prognosis is almost uniformly good. A very few fatalities are recorded, due to nephritis or endocarditis.

Treatment.—The patient should be isolated when practicable, to prevent the spread of the disease. Rest in bed is indicated, especially on account of the danger of nephritis, and should be maintained until the temperature is normal. The diet should be light and such as the patient can take readily. Antiseptic sprays and gargles may be used to advantage, with ice-bags or warm fomentations to relieve the pain in the neck. Various authors recommend antipyretics, quinine, phenacetine, etc. Calomel, recommended by most observers, is condemned by Park West as weakening the patients and causing delay in convalescence. Tonics, fresh air, and good food are indicated in convalescence. Iron may be necessary in cases with secondary anemia.

INFECTIOUS JAUNDICE[1]

Synonyms.—Epidemic Catarrhal Jaundice; Weil's Disease; Bilious Typhoid.

Definition.—There are several types of acute infectious icterus characterized in general by a sudden febrile onset with pronounced gastrointestinal symptoms and rapidly developing jaundice, sometimes accompanied by enlarged and tender liver and spleen, with albuminuria and severe nephritis. In some epidemics delirium and coma are frequently observed. The course is from a few days to three weeks, and usually

[1] An excellent article is by Knoepfelnacher, *Ergebnisse der inner. Med.*, 1910, v, 205.

terminates in recovery. In 1886 Weil[1] published the first thorough study of the epidemic type and emphasized the acute onset, rapid and extreme development of jaundice, with tender and enlarged liver and spleen and accompanying nephritis, and pointed out the tendency to relapse. Many authorities demur to the designation of Weil's disease as separate from other types of benign infectious jaundice.

Etiology.—The question of the specific organism can as yet hardly be considered settled. Jaeger described a bacillus of the proteus group as the pathogenic factor in a garrison epidemic at Ulm in 1892. This organism, which he has named *Bacillus proteus fluorescens*, has been found by other observers in Germany and elsewhere. It is to be noted that other organisms have been reported from cases presenting the same clinical picture, especially the colon bacillus and other members of the hog-cholera group. Cases reported in the French literature have frequently been described as colon bacillus septicemia.

The disease is most frequent in the second and third decades and nearly 90 per cent. of the reported cases are males. A number of single cases and small epidemics affecting children have been noted (Weiss, Wassilief, Kiesel, and others) and some even in sucklings. The incidence is greater in the spring and summer months and in wet seasons. Those exposed to foul water, as workers in ditches and sewers, soldiers, agricultural laborers, and butchers, seem most frequently affected.

Pathological Anatomy.—Relatively few of the cases have come to autopsy, and of these some are undoubtedly icterus gravis or acute yellow atrophy. In fact, the group here described stands between simple catarrhal jaundice and grave destructive icterus, and there are all grades of transition toward the extremes. The pathological findings in general are marked jaundice of the tissues, with wasting, slight enlargement and cloudy swelling of the liver and spleen, sometimes with small foci of fatty degeneration in the former. The kidneys show a diffuse, tubular nephritis; no characteristic lesions of the intestine. Hemorrhages into the spleen and the serous cavities have been described. The small bile ducts are swollen and the mucosa degenerated.

Symptoms.—The onset is usually quite sudden and may be fulminant. Occasionally, however, prodromata, lassitude, headache, and loss of appetite precede the attack. The patient is seized with a rigor or there may be no chill. The temperature rises quickly to 103° or 104°, and the pulse is at first rapid and then slower after the appearance of the jaundice. Gastro-intestinal features are prominent at the onset, griping pains, nausea, and vomiting, and diarrhœa being common. In the course the stools may be first rich in bile and then clay colored. The nervous manifestations are also marked. Headache, dizziness, pains in the back, and especially in the calf muscles, may be intense. Prostration is rapid and extreme. Delirium is very frequent. Drowsiness and even coma may rapidly follow and the picture is like the "typhoid state," developing, however, more rapidly than in typhoid fever. Jaundice begins to appear about the second to the fourth day and rapidly

[1] *Deut. Arch. f. klin. Med.*, 1886, Band xxxix, p. 209.

becomes intense. The liver is slightly enlarged and tender and the spleen usually swollen. Herpes, diffuse or macular erythema, and urticaria may be seen. A tendency to hemorrhage is frequently noted. Epistaxis, slight hemoptysis, bleeding from the stomach or bowels, petechial eruptions and bloody exudates into the serous cavities and joints have been described. The albuminuria is usually of a considerable grade, and hyaline and epithelial casts in large number are usually present. The urine contains great quantities of bile pigments and sometimes red blood cells. Bronchitis is conspicuously infrequent. After four to nine days of rather steady elevation the temperature begins to remit markedly and falls slowly to normal in about five to six days. The jaundice and the muscle pains disappear more slowly; the latter may be marked well into the convalescence. The liver and spleen tumors subside and the nephritis gradually clears up.

Convalescence is usually protracted and the loss of weight is often very great, from ten to twenty pounds in adults during the febrile period. In a large proportion of the cases (about 40 per cent.) there is a relapse occurring from three to eight days after the temperature first becomes normal. It is a milder repetition of the initial paroxysm and lasts five to eight days. The persistence of the splenic tumor after the first paroxysm is thought to be indicative of a relapse.

There are many abortive and mild cases which would hardly be recognized except during epidemics. Fatal cases are rare and some of those so described are not properly included in this group. Some few die from acute nephritis and uremia, others with heart failure or toxemia of the central nervous system, and, more rarely still, after the development of pneumonia.

Diagnosis.—Weil's disease is a type of infectious jaundice in which fever, enlargement of the spleen and liver, nephritis, and muscular pain accompany the icterus. But there are so many similar sporadic and epidemic cases in which one or more of these features may be wanting that it seems hardly justifiable to separate this group sharply from all the others. Simple catarrhal jaundice lacks the features of general infection. The demonstration of the specific spirillum of Obermeier will differentiate relapsing fever. The resemblance to dengue and mild cases of yellow fever is rather striking, although the greater joint involvement and widespread epidemic character of the former should prevent serious confusion, while the exclusion of the specific intermediate host, *stegomyia*, and the frequent occurrence of epidemic jaundice in regions where yellow fever is unknown would reasonably exclude the latter possibility. From icterus gravis and acute yellow atrophy only the course of the disease and the absence of destruction of the liver can fully differentiate these benign cases, and there is, in fact, a gradual merging of the types and no distinct borderline.

Treatment.—Absolute rest is necessitated by the patient's condition and should be protracted into convalescence. A diet of milk and light broths should be maintained during the febrile period. Hydrotherapy is often helpful, forced water drinking, enemata, and subcutaneous infusion of salt solution being indicated in the more toxic cases. Cool

baths and ice-bags during the height of the fever are to be recommended. Warm stupes and fomentations greatly relieve the muscular pain. Strong purgatives and alcohol are contra-indicated and intestinal antiseptics are of little or no value. Small doses of calomel may be useful in special cases. After convalescence is established the diet should be increased gradually and every effort made to build up the patient's strength and repair the tissue waste.

MILIARY FEVER

Synonyms.—Sweating Sickness; Suette Miliare; Schweissfriesel.

Definition.—An acute infectious disease occurring in localized epidemics of short duration and exceedingly variant severity. The onset is abrupt, with or without prodromata, the cardinal symptoms being fever, excessive continuous sweating, great anxiety and oppression, with rapid and often tumultuous heart action and respiratory distress. On the third or fourth day an erythematous rash appears, accompanied by miliary vesicles and sudamina. With the appearance of the rash the fever subsides gradually and slow recovery follows, or death may ensue in a few hours to three or four days after onset.

There is little reason to doubt the substantial identity of the miliary fever of today with the "sudor anglicus" or sweating sickness which swept over England in five epidemics between 1485 and 1557. These plagues differed from the present type of the malady in their wide and rapid dissemination, briefer course, greater mortality, and the absence of the rash. Detailed historical and statistical accounts will be found in the writings of Hecker, Haeser, Hirsch, and Immermann.

Etiology and Pathological Anatomy.—Many theories have been advanced to explain the origin and localization of the disease—among others, soil and weather conditions, miasma, and malaria. In general the disease appears more frequently in the spring and summer months. It appears suddenly in localized epidemics which are of very brief duration, often not more than two weeks. In this time a very large proportion of the population may be affected. All ages and both sexes are susceptible, although it is more prevalent among the robust. That the frequency is greater in women seems settled. The lethality in modern epidemics varies from 33 per cent. to zero and may be even so variable in different places during the same epidemic. There is some evidence in favor of the transmission of the malady by direct and even by indirect contagion. Cultures from the vesicles, the blood, and organs have not led to the discovery of the causative factor.

There is nothing striking about the changes in the viscera. The spleen is somewhat engorged and shows cloudy swelling. The same is true, to a less degree, of the liver and kidneys. The heart is flabby and shows marked segmentation and fragmentation. There is slight swelling of Peyer's patches and often some blood in the intestine. The intestinal miliaria described by some writers may be due to the gas bacillus. The nervous system shows no distinctive changes beyond

hyperemia and slight increase in the cerebrospinal fluid in fulminant cases. Parrot and others made repeated attempts to inoculate healthy individuals with the contents of vesicles, but were unsuccessful.

In 1905 an epidemic of 126 cases occurred in Austria and is reported by Scholz.[1] In the following year an epidemic of 6000 cases was observed by Chantemesse[2] and others in Northern France. In their study, they were led to advance the hypothesis that the disease is transmitted by fleas from field mice. They strongly oppose the contagion hypothesis. Saizy[3] contributed a good clinical study of the same epidemic, with temperature charts and a careful analysis of the sequels of the disease.

Symptoms and Course.—The disease may be preceded by a brief prodromal stage, with malaise, headache, vertigo, muscular weakness, joint pains, and dryness of the mouth, sometimes nausea and vomiting. These usually precede the attack by a few hours only, although occasionally of one or two days' duration. Often they are altogether absent. The onset is sudden and in a great proportion of cases occurs in the night. The first symptom is sweating, although this may be preceded by a slight chill. At the same time the temperature rises and the patient feels a burning heat in the skin despite the extreme sweating.

The temperature varies with the severity of the epidemics and the individual cases. Averaging 102° to 103°, it frequently reaches 105° to 106° in severe cases, and may be even higher. The pulse rate is increased out of proportion to the temperature and is further peculiar in its variability coincident with the cardiac paroxysms characteristic of the disease. The heart beat during these paroxysms is irregular and almost delirious. The palpitations cause the patient great anxiety. Marked pulsation and a peculiar sensation of constriction in the epigastrium are among the classical symptoms. This is generally constant to a greater or less degree and increased in paroxysms of variable intensity. Associated with it there may be tenderness on pressure. A feeling of laryngeal occlusion and impending suffocation is also very common. These phenomena are subjective and of nervous origin as examination of the heart and lungs discloses no abnormality.

Other nervous features associated with the primary or sweating stage, although of less importance, are great prostration, delirium, clonic convulsions, and cramps in the hands and legs. The lips and tongue are dry, the breath foul, and there is marked anorexia with great thirst. Often nausea is present and less commonly vomiting. The urine is greatly reduced in volume and temporary anuria is often observed. The low output persists until the sweats cease, when there is often a sudden critical discharge of urine rich in salts. Albuminuria is not common. There is no leukocytosis. Epistaxis and hemorrhages from the bowel occur frequently in some epidemics, although the bleeding is rarely serious. The rash may have a purpuric character in such cases. There is commonly moderate enlargement of the spleen with little or no increase in the size of the liver.

[1] *Zeit. f. klin. Med.*, 1906, Band lix, pp. 542–564.
[2] *Bull. Acad. méd. de Paris*, 1906, 3d Serie, Tome lvi, pp. 293–296.
[3] *La clinique de Paris*, 1906, Tome i, pp. 435, 437, and 787–789.

The sweating is the most striking and persistent feature of the disease. It is extraordinarily great in amount and differs from the sweating of most febrile diseases in appearing with the onset of fever, continuing during the fever, and increasing with increase of temperature. It is probably due to toxic excitation of the medullary centres.

The eruption appears on the third or fourth day and is seen first on the neck and back, under the breasts and axillæ, and between the thighs. A general erythema is present, in addition to which appear (*a*) sudamina (miliaria alba or crystallina), (*b*) red papules becoming vesicular (miliaria rubra), (*c*) petechiæ of variable size (purpura miliaria). The appearance of the eruption is preceded by itching. The red papulovesicular type is most frequently observed, with usually some sudamina; the purpuric type is not seen so often and occurs in the cases with other hemorrhagic manifestations. Vesicles are also frequently found on the mucous membranes of the conjunctiva, nose, and mouth. The rash may come out rapidly and cover the whole body in twenty-four hours or slowly and in successive crops. Thus desquamation may be advanced in the regions first affected, while other areas show the early stages.

The eruption stage marks a crisis and the symptoms above noted usually abate gradually after its appearance. The fever drops with a rapidity proportionate to the development of the rash. The nervous and digestive disturbances become less marked and the sweating more slowly lessens, disappearing only with convalescence.

Convalescence is very slow in mild as well as in severe cases. There is usually great weakness and anemia and loss of weight. Tremor, cardiac arrhythmia, insomnia, and general nervousness are apt to persist for some time and months may elapse before the patient is fully restored.

While the course of the disease is usually favorable, it is not always so. In the fulminant cases death may ensue within forty-eight hours from the onset. In such cases extreme hyperpyrexia, dyspnœa, and very rapid pulse, with precordial pain and constriction, are characteristic. Delirium and death from suffocation end the attack often before the rash has appeared. In other cases which begin mildly a similar development may take place suddenly on the third or fourth day before the appearance of the rash. More rarely sudden collapse occurs, with cyanosis and death in a few minutes.

In the second stage there is occasionally death following multiple hemorrhages from the nose and intestinal tract. Recrudescence is sometimes observed during the second stage, accompanied by intensification of the fever, sweating, and nervous symptoms. Relapses are extremely common in the first two weeks, and are usually milder than the primary attack.

Diagnosis.—This is not difficult with typical cases. The abrupt onset, sweating with fever, nervous phenomena, and the vesicular rash are peculiar to this malady. Very mild and atypical cases may be confused with measles.

Prophylaxis and Treatment.—As the evidence points to the possible contagious character of the disease, patients should be isolated and rigid disinfection of house and clothing enforced. The therapy is symp-

tomatic. The patient should be lightly covered and the room thoroughly ventilated. The wet clothes should be frequently changed. Cold packs give much relief during the hyperpyrexia and diminish the nervous symptoms. The diet should be bland and mostly liquid, with large amounts of water. In serious cases the symptoms must be met as they arise. Atropine in guarded doses may be helpful in cases of excessive sweating and anuria. Grave nervous phenomena and cardiac delirium are best met by the careful administration of morphine. The efficacy of quinine is very doubtful. Careful dieting and the exhibition of iron and tonics aid complete restoration during convalescence.

ROCKY MOUNTAIN SPOTTED FEVER

Synonyms.—Tick Fever of the Rocky Mountains; Piroplasmosis Hominis; Black Fever; Blue Disease.

Definition.—An acute infectious disease of man characterized by sudden onset, with chill, continued fever, headache, severe pains in joints and bones, and a macular eruption, becoming petechial, which appears first on the ankles and wrists, later spreading all over the body. The disease known as "spotted fever" has been observed in the Bitter Root Valley for more than thirty years, or since the early days of permanent occupation by white settlers, the first recorded cases occurring at Woodside, Montana, in 1873.

The disease is endemic in the Bitter Root Valley of Montana, appearing in the spring months, and occurs also in the neighboring mountainous parts of Idaho, Wyoming, and Nevada. It affects all ages and both sexes, and is, in the light of the evidence so far collected, not contagious. The mortality varies with location and from year to year, averaging 70 per cent. in Montana, but very much less (1 to 3 per cent.) in Idaho. It can be conveyed by the bite of the "wood tick," *Dermacentor andersonii* (Stiles), and is transmissible experimentally to monkeys, guinea-pigs, and rabbits.

Etiology and Pathology.—The incidence is striking as to localization and time of appearance. It occurs only in the high valleys of the circumscribed mountain regions above noted and in the spring and summer months, the cases appearing as early as March and as late as July, but the greater number falling in the months of May and June. All ages and both sexes are susceptible, but the incidence is greater in males between the ages of twenty and forty years and among those whose occupation leads them afield and into the forests; cattlemen, farmers, lumbermen, and miners are most apt to be affected. The cases appear singly in widely separated places and there is little or no evidence to point to family or house infection.

The first pathological study of the disease was made by Wilson and Chowning[1] in their report to the Montana State Board of Health. They described bodies in the fresh and stained blood which they held

[1] *Journal of the American Medical Association*, 1902, xxxix, 131–138.

to be hematozoa and named *Pyroplasma* (*Piroplasma*) *hominis*. Subsequent investigation, however, by Stiles, King, Ashburn, Ricketts, and others has failed to substantiate the findings. Nor have Wilson and Chowning been able to demonstrate their organisms in a convincing manner. Similar bodies were described by these authors in the blood of the burrowing squirrel or "gopher" (*Citellus columbianus*), and they first suggested the role of the tick in conveying the disease. They also described the transmission of the piroplasma to rabbits experimentally by injecting blood from patients. Stiles[1] (1905) published a zoölogical study of the disease and a complete bibliography. He was unable to find any piroplasma in the blood of typical cases during life or postmortem. In general the piroplasma theory has met with lack of confirmation and skepticism.

In 1906, Ricketts,[2] succeeded in transmitting the disease to guinea-pigs and monkeys by intraperitoneal injection of the blood of patients suffering from spotted fever, and finally established a constant transmission in laboratory animals.

King[3] and Ricketts[4] separately demonstrated beyond doubt that the ticks, *Dermacentor andersonii* (Stiles), male and female, are capable of transmitting the infection by their bites. Whether they are necessary intermediate hosts or play a purely mechanical role is not yet determined. These ticks appear with the first warm days of spring and begin to disappear in June.

Experimental animals, surviving one attack of the disease, show a high degree of immunity to further inoculation. According to Ricketts'[5] the virus is destroyed at a temperature of 50° C. in half an hour. Desiccation rapidly deprives the blood of its infectious power, but the virus can apparently withstand a low temperature for a number of days. The infectious agent does not pass through Berkefeld filters.

The pathological findings reported by Wilson and Chowning, Anderson, Ricketts, and subsequent writers include as the main features extensive petechial involvement of the skin confluent over dependent areas, and most abundant on the arms, legs, and back. The capillaries of the skin are engorged and there is some extravasation of blood in the rete mucosum. Evidence of recent tick bites is reported in a number of cases. The cerebral and spinal meninges were normal or showed slight hypostatic congestion. No meningitis was found in any case. The lungs were normal or with hypostatic congestion; the heart flabby and friable, with small petechiæ under the epicardium. The stomach and intestines were normal. The spleen is greatly enlarged, dark in color, and diffluent, the Malpighian bodies are obliterated, and there are many phagocytic leukocytes with red blood cells, but no free pigment.

[1] *Bulletin No.* 20, *Hygienic Laboratory of United States Public Health and Marine Hospital Service.*

[2] *Journal of the American Medical Association*, 1906, xlvii, 33–36.

[3] *Public Health Reports*, July 27, 1906.

[4] *Journal of the American Medical Association*, 1906, xlvii, 358 and 1067–1069; Carpenter Lecture, *Medical Record*, New York, 1909, lxxvi, 842, also *Ricketts' Memorial Volume*, University of Chicago, 1911.

[5] *Journal of Infectious Diseases*, 1907, iv, 141–153.

The liver is enlarged and shows extensive fatty infiltration; the pancreas is also increased in size. In every case the kidneys were large and red with small hemorrhages under the capsule and in the pelvis. The cortex was swollen and congested, but not adherent; the pyramids red and sharply defined; general cloudy swelling was evident microscopically.

The experimental lesions in guinea-pigs and monkeys correspond to the above findings, although the skin involvement is much less marked, guinea-pigs showing extensive purpura of the genitalia and monkeys in some instances a petechial eruption quite like that in man.

Symptoms and Course.—The incubation period is from three to ten days and during this time there is increasing malaise, with pain in the bones and muscles. There is ordinarily a severe chill at onset which may recur. Nausea and headache are common. The bowels are constipated and pains in the limbs are quite characteristic. The tongue is furred and there is a yellowish tinge to the conjunctivæ, with deepening jaundice during the course. Nose-bleed is not infrequent at onset and may be severe in the second week. The temperature rises rapidly after the chill and is continuous, with but slight daily variations. It usually reaches 103° to 104° on the second day and may continue to rise in the following week and, in fatal cases, be as high as 105° to 107°. In the milder cases the temperature declines slowly after the tenth to the twelfth day and reaches normal during the third week.

The pulse is characteristically very rapid, ranging from 110 to 140 in average cases and much higher in very severe ones. At first full and strong it becomes thready as the disease progresses. The respiratory rate is also increased, averaging 36 or more per minute. Slight bronchitis is common and pneumonia is a well-recognized complication.

The blood shows a steady diminution of red cells and hemoglobin during the fastigium and defervescence with regeneration after the temperature falls. The leukocytes are normal or moderately increased.

The digestive system may show little or no disturbance during the early part of the disease, but nausea and vomiting are apt to appear in the second week and may be persistent and excessive in fatal cases. Enlargement and tenderness of the spleen are marked and appear early. The liver is also palpable just below the costal border. There is no general abdominal tenderness, as a rule. Hemorrhages from the nose, mouth, stomach, and bowels are not uncommon. Bloody effusions into the joints are also reported. The urine is scanty and high colored, with a trace of albumin and hyaline, epithelial, granular, and blood casts, but hemoglobinuria is absent.

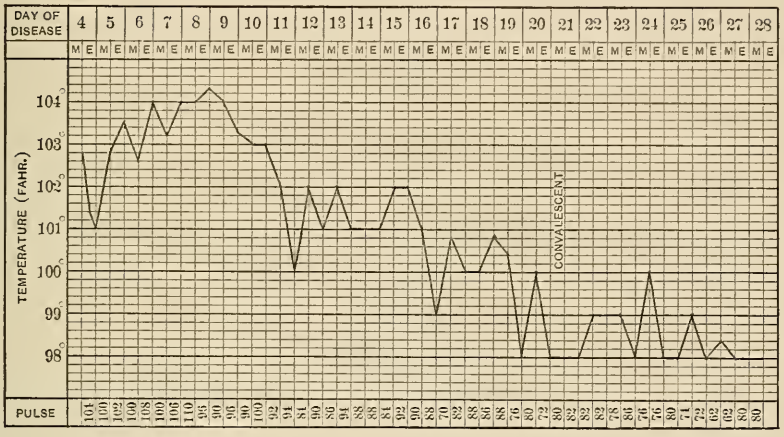
Restlessness, irritability, pain, and hyperesthesia with photophobia are common nervous symptoms. In severe cases stupor with low delirium is frequent and coma usually precedes death. Slight opisthotonos is reported for a few cases, but muscular rigidity and Kernig's sign are absent. Convulsions have been noted rarely in children.

The rash appears on the second to the seventh day after onset, most commonly on the third day. It is first seen on the wrists and ankles, spreading toward the trunk, and is found on the forehead and breast,

but especially thick over the back. The abdomen shows fewer spots and is involved later.

In the severe cases the palmar surfaces of the hands and feet and also the scalp may be thickly covered with the eruption. At their first appearance the spots are bright red, disappear on pressure, and vary from 1 to 6 mm. in diameter. These macules become steadily darker and definitely petechial. By the seventh to the tenth day they have usually reached the fullest development when the fever is also at its height. At the same time icterus is marked and the spots may be confluent over dependent parts, giving a mottled appearance.

FIG. 43



Rocky mountain spotted fever. Temperature curve. (Wilson and Chowning.)

With the decline of the fever the spots fade, leaving a stain in the skin. Exacerbations or sweating may cause them to reappear and during convalescence a warm bath or exercise will bring them out. Often in severe cases there is gangrene of the skin over the toes, fingers, elbows, ears, and frequently scrotum and penis. Œdema is also noted over the head, face, and dependent parts. Desquamation begins when convalescence is well advanced and is general, although most marked, on the hands, feet, and face. Convalescence usually begins about the fourth week and is generally slow. In a very few cases relapses have been noted. The principal complications are gangrene, above noted, and lobar pneumonia. Immunity is conferred by one attack.

Diagnosis.—To those who have seen the disease its recognition is easy. Its endemic and seasonal occurrence, the character of the rash and associated pain and nervous phenomena are sharply defined. From typhus fever it is distinguished by its occurrence in isolated cases in scattered communities and its non-contagious character. The onset in typhus is abrupt and the decline by crisis. In typhoid fever the lower fever, slow pulse, diarrhœa, Widal test, and positive blood cultures make the distinction easy. In cerebrospinal meningitis, the

greater prevalence in children, frequent absence of rash, more intense nervous symptoms, and the demonstration of the organism by lumbar puncture render the differentiation fairly easy. A mild type without any rash is said to exist. Its diagnosis is, however, not at all clear.

Prognosis.—While delirium and marked nervous features are considered unfavorable, little can be premised from the severity of the eruption or the height of the fever. Death occurs most frequently between the sixth and twelfth days and patients surviving the second week are likely to recover. The mortality is greater among the old and less in children.

Treatment.—There is no specific remedy and the therapy is symptomatic. Good surroundings with careful nursing are important. The patient should be protected from noise and have the room darkened. The diet should be liquid or soft in character until the decline of the fever. Sponge baths of cool or tepid water are helpful in reducing the nervous phenomena and lowering temperature. Phenacetin and other antipyretics are in common use. Free purgation with calomel and saline cathartics, supplemented by enemata when necessary, is recommended by most observers. Morphine may be necessary for the relief of excessive pain. The forcing of water and use of diuretics is indicated and saline infusions may be necessary in severe cases. The efficacy of quinine is not settled, the opinions being widely divergent.

PSITTACOSIS

Definition.—An epidemic disease of parrots distinguished by general debility, loss of appetite, and chronic enteritis, with a high mortality. The same name is also applied to a disease in man characterized by onset like typhoid fever, with signs of severe atypical pneumonia. This has occurred in house epidemics and been ascribed to contagion from sick parrots.

Etiology and Pathology.—In the Paris epidemic of 1893, Nocard isolated a bacillus from the dried wings of parrots dead of psittacosis and showed that it was very pathogenic for parrots, pigeons, fowls, and laboratory animals. Other observers have failed to find the organism in man, but some have succeeded in isolating it from the bodies of parrots. The pathological findings in parrots show enteritis with cloudy swelling of the liver, spleen, and kidneys, but no pulmonary involvement. In men the principal feature of the fatal cases has been the presence of pneumonia with signs of general infection. Cultures have yielded the pneumococcus, streptococcus, colon bacillus, and other organisms. Nocard advanced the theory that the bacillus of psittacosis prepared the way for secondary pneumococcus infection, and this view is generally held by the French observers.

The possibility that this disease may be transmitted from parrots to man cannot be denied when the incidence in relation to the sick parrots and the simultaneous infection of whole families are taken into consideration. The bacteriological findings are very contradictory and

unconvincing. Exactly similar house epidemics of atypical pneumonia have been recorded entirely unrelated to the disease in parrots.

Symptoms and Course.—The malady resembles typhoid fever complicated with pneumonia. The incubation period is uncertain, varying from seven to twenty-five days in different reports. Dubief gives the average as seven to ten days. The onset is variable: in some cases sudden, with chill, as in pneumonia; in others gradual, with headache, malaise, photophobia, loss of appetite, nausea, constipation, great lassitude, and weakness. In those who practise mouth-to-mouth feeding of parrots the initial involvement may be a diphtheroid stomatitis, with enlargement of the submaxillary glands.

The rise of temperature is usually rather rapid, reaching 102° to 104°. The fever is continuous with daily remissions. The pulse varies from 100 to 120. From the first there is cough, mucopurulent or bloody sputum, and increased respiratory rate. On auscultation, fine moist rales are heard throughout both lungs. There is usually no evidence of consolidation at the time of onset. The tongue is dry and furred and the breath foul. Abdominal symptoms are not marked. The spleen is, however, enlarged and, rarely, scattered rose spots or petechiæ are seen. Diarrhœa or constipation may be present, the former being more common. Nausea and vomiting are not usual except at the onset. The patient is dull and stupid, with more or less marked delirium. In uncomplicated cases the duration is fifteen to twenty days and the prognosis is generally favorable. With pneumonic symptoms the aspect is graver, and to this factor the high mortality is due. The pneumonia may be lobar or lobular and involve different areas in succession.

Diagnosis.—The recognition of the disease is difficult, and depends principally on the association of house epidemics with the presence of diseased parrots. The clinical picture is much like atypical pneumonia. Severe influenza has many points of similarity and the first Paris cases were so diagnosticated by Dujardin-Beaumetz.

Prognosis.—The average mortality is between 35 and 40 per cent., being highest in old people and notably less in children.

Treatment.—In view of the possible agency of the parrot in conveying this infection the handling of sick birds should be discouraged. Cleanliness and disinfection of the cages should be carefully observed. The patients should be isolated as a precautionary measure. Tub baths and cold packs are highly recommended by the French observers, who treat the cases throughout like typhoid fever.

FOOT-AND-MOUTH DISEASE

Synonyms.—Aphthæ Epizoöticæ; Aphthous Fever; Maul und Klauenseuche; Fièvre Aptheuse.

Definition.—An infectious disease of cattle and other domestic animals, the characteristic features of which are moderate fever, disappearing with the development of a vesicular eruption on the mucous membranes of the mouth and on the skin above the hoofs and between the toes.

Ulceration follows, with salivation and great tenderness of the affected parts. Loss of appetite and great emaciation accompany this stage. Healing is slow, but most animals recover. Fatal apoplexy is not uncommon and death from septic infection of the sores is also well known.

The malady is transmissible to man through unboiled milk or butter and cheese, and also directly from the saliva or contents of the vesicles of infected animals gaining entrance through abrasions of the skin. It is especially frequent in children and in those whose work brings them in contact with diseased cattle.

The aphthous epizoötic was first described in human beings in the eighteenth century. Epizoötics have been frequent and entailed great losses throughout Italy, Germany, and France. In America the disease has never been widely prevalent. Local outbreaks have been recorded in New England and the Middle States in 1870, 1884, and 1903, and in Pennsylvania in 1908. Human infection has constantly accompanied the epizoötics, and its incidence is probably much greater than the reports indicate, as the milder cases were not seen.

Etiology and Pathological Anatomy.—The specific organism is still unknown despite the great amount of work devoted to its discovery. Bacilli, cocci, streptothrices and protozoa have been described by different observers as the causative factor. In 1898, Loeffler and Frösch[1] demonstrated that the virus was ultramicroscopic and passed through the finest porcelain filters. The filtered lymph, free from all demonstrable bacteria, was capable of producing the typical lesions in all the animals susceptible to natural infection and transmissible indefinitely from them to others. This discovery discredits absolutely all the findings of organisms of whatever sort.

The infection is spread readily by contact with sick animals or by the dung or litter or the use of stalls or drinking troughs previously used by them. It is also communicable from one species of animal to another; cattle, horses, sheep, goats, swine, deer, and even dogs and fowls are susceptible. The demonstration by Mohler and Rosenau[2] that the 1908 outbreak was due to the importation of contaminated vaccine is of great interest and importance.

The portals of entry for natural infection are not clearly established, but animals may be infected by injection of lymph from the vesicles into the blood, peritoneal cavity, muscles, and digestive tract, or by rubbing on the scarified mucosa of the mouth. Cutaneous and subcutaneous infection is irregular and uncertain. Two to three weeks after the beginning of the attack most animals show a greater or less degree of natural immunity, which is, however, of uncertain duration. An antibody capable of protecting against a certain amount of virus is present in the serum during this time. This immunity can be greatly increased in heifers and young swine by repeated injection of virus in increasing doses, and a protective serum conveying a brief passive

[1] *Centralbl. f. Bakt. u. Parasit.*, 1898, Band xxiii, abt. i, pp. 371–391 u. ff.
[2] *Bureau of Animal Industry Circular* 147, 1909.

immunity to other animals has been made (Loeffler and Uhlenhuth). Active immunization has not been successfully carried out.

Of the typical morbid anatomy, apart from complications, little is known, as few animals die from this cause directly. The vesicles form in the rete mucosum and the subsequent ulceration is usually completely healed without scar by extensions of the epithelium over it. Animals dying during the disease have shown vesicles in the œsophagus, trachea, and bronchi. The ulcers on the feet are especially liable to secondary infection, which may lead to severe inflammation of the matrix and separation of the hoof, arthritis, bone necrosis, and general pyemia.

Symptoms and Course.—In man the disease sets in with fever after variable incubation periods of two to ten days. The fever is usually not very high, but may reach 104° and be accompanied by a shaking chill. Loss of appetite, languor, pains in the muscles, back, and head, with cramp-like pains in the abdomen, nausea, and vomiting are common.

The primary seat of infection in man is most frequently the mouth, due to drinking infected milk. The mouth feels hot and dry and there are areas of hyperemia over the lips, base of the gums, margin of tongue, and mucosa of the cheeks. The vesicles form about two to three days after the initial symptoms and are at first small and discrete, but tend to enlarge rapidly and become confluent. They may extend over the whole buccal mucosa and into the pharynx, larynx, œsophagus, and trachea. On the skin the blebs are often found about the mouth and nose. The conjunctiva and cornea may be involved and the skin between the toes and fingers is frequently affected. Among those working with sick cattle the borders of the nails are often attacked and severe panaritium may follow with secondary pyogenic infection. In severe cases the vesicles may be distributed over the whole body, especially about the breasts, thighs, gluteal folds, and genitalia.

With the development of the vesicles the temperature falls. At the same time the tongue and lips swell and there is difficulty and pain in swallowing with marked salivation. There may be also a profuse nasal discharge. The content of the vesicles is at first clear, but soon becomes purulent and invaded by the mouth bacteria. The vesicles are easily broken and leave weeping, shallow ulcers, which are very painful when touched. This painful ulceration of the mouth and gullet often leads to serious inanition through the refusal of food. Speech may also be difficult. The submaxillary and sublingual lymphatics and occasionally the salivary glands may be swollen and painful. In the vesicular stage there is often colic and diarrhœa or bloody stools in children.

The course of the disease when uncomplicated is generally mild and favorable. The ulcers become crusted over and gradually covered with new epithelium, leaving no scars except where there has been pyogenic invasion of the corium and subcutaneous tissue. The average duration is two weeks from the onset, although very mild cases may be well in less time and more severe ones last six to eight weeks. In young children the danger is greater from the severe disturbances of nutrition, rendering them liable to severe gastro-enteritis and even death from inanition.

Diagnosis.—In any case of aphthous disease the history should be carefully noted, with special reference to the presence of foot-and-mouth disease in the neighborhood or at the source of milk and butter supply. These facts with the characteristic onset and the superficial rapidly developing vesicles would make the diagnosis certain. The common aphthæ in children are small, round, yellowish, discrete, and unaccompanied by acute general symptoms. Stomatitis ulcerosa is distinguished by the extensive and deep infiltration and rapid necrosis, especially of the gums. Inoculation of the contents of the vesicles into the mouths of sheep or swine would make the diagnosis definite. The hands may be the primary seat of the vesicles in those who work with cattle.

Treatment.—Prophylaxis is of primary importance. Isolation and slaughter of infected herds and condemnation of the dairy products, with thorough disinfection of the stalls and troughs should be enforced. The milk is rendered innocuous by heating to boiling. But milk from sick cattle should not be used, even if it be sterilized. The injection of bichloride of mercury has been recommended by Baccelli for the treatment of cattle and widely used in Italy. The German commission reported adversely on the Baccelli treatment, and think it may be harmful. It is not applicable to man.

In man it is well to isolate the patient and apply local remedies to the ulcers. Chlorate and permanganate of potassium are recommended as mouth washes and the ulcers may be touched with silver nitrate or copper sulphate. Drying powders may be applied to the external lesions. Special attention is given to the diet, and in severe cases or in young children, feeding by nasal or stomach tube or nutritive enemata may be indicated.

MILK SICKNESS

Synonyms.—Trembles; Slows; Puking Fever.

Definition.—A disease primarily of herbivorous animals and transmissible to man or other animals feeding upon the milk or flesh of infected individuals. The disease is characterized by gradual loss of appetite, obstinate constipation, drowsiness, muscular tremor, and convulsions; or it may be latent and develop fulminantly in such cases by forcing the animal to vigorous muscular exertion.

This remarkable disease is known only in certain widely scattered districts of the United States, including the upper and middle parts of the Mississippi Valley, the mountain regions of the Southern States and the Southwest. The report of Jordan and Harris[1] gives the history and literature.

Etiology and Pathology.—The disease is not confined to any time of year, but is more prevalent in the summer and fall, and apt to be more severe in dry years. The infected pastures are never increased in area, but seem rather to decrease with time. Areas formerly free have not been known to become infected. Clearing and cultivation, if persisted in, will render the pastures safe. Jordan and Harris have isolated an

[1] *Journal of Infectious Diseases*, 1909, iv, 401.

organism, *B. lactimorbis*, from the milk and tissues of infected animals. This organism injected into cats and dogs produces some of the clinical and pathological changes found in milk sickness.

The pathological findings in cattle or in animals secondarily infected are the same: some injection with great contraction of the intestines and stomach, enlargement and softening of the liver and spleen, while hemorrhages and exudation into the serous cavities are constant. There is often great engorgement of the cerebral vessels, with fibrinous exudation on the meninges and softening of the brain.

Symptoms.—In man the disease comes on after an incubation period of three to ten days, with languor, loss of appetite, and extreme constipation. Headache, tinnitus aurium, and muscular pains may be present in some epidemics and absent in others. There is great thirst, with nausea and persistent vomiting. In severe cases the vomitus is of a bile-tinged and soapy character and may contain blood. The tongue is swollen, flabby, shows the impress of the teeth, or may be protruded from the mouth and coated with a whitish fur. The breath has a peculiar, sweetish odor, which is quite characteristic. The pulse is quick, full, and soft, and there is no fever or only a very slight rise of temperature. The cerebral symptoms may be varied. Great irritability, convulsions, and marked delirium are characteristic of some epidemics, while in others drowsiness and coma are more common. The abdomen may be moderately distended and is doughy on palpation, and there is often marked epigastric pulsation. The urine is scanty, pale, and commonly shows a trace of albumin. In fatal cases death may occur in from three to ten days after the initial symptoms, coma and gradual cardiac failure being the terminal features.

The mortality varies greatly in different epidemics and may be from 10 to 90 per cent. The milder cases show a slow abatement of the symptoms, sometimes with critical discharges and a long convalescence. In this stage the slightest muscular exertion may bring on typical "trembles," as seen in cattle. Very often the patient is unable to work for months; others are more or less permanently incapacitated. Progressive dementia is said to have followed severe attacks.

Diagnosis.—In regions where "trembles" in cattle is prevalent, the recognition offers little difficulty, and in any case the occurrence of the characteristic nausea and vomiting, great thirst, enlarged tongue, and obstinate constipation without fever would make the diagnosis probable and lead to a careful investigation of the milk, butter, and meat supply. Cases are apt to occur simultaneously in families. Occasionally severe gastro-enteritis or typhoid fever may be mistaken for milk sickness in regions where this prevails. The history and course should soon lead to a correct diagnosis.

Treatment.—Absolute rest and free purgation, preferably with salines or castor oil, persistently administered until effective, give excellent results. Stimulation is indicated in most cases. During convalescence strychnine and iron are advised. The patient must avoid severe muscular exertion for a long time lest he precipitate an attack of "trembles."

RAT-BITE DISEASE[1]

Synonyms.—Sodóku; Rat-bite Fever; Rattenbisskrankheit.

Definition.—An infectious disease, following rat bite, characterized by recurrent paroxysms of fever, muscular pain, and erythema.

Distribution.—Sodóku is described in the earliest medical literature of Japan. It is endemic in the four chief islands, and, while not common, is more prevalent there than in any other country, so far as known. Owing to the frail construction of the houses, rats enter freely and sleeping persons are frequently bitten. Only a small percentage develop the rat-bite disease. The more recent Japanese observers conclude that diseased rats of both field and house species may convey the infection. A number of cases have been described in the United States and a few in England (Horder, Middleton, Cruikshank), Italy, and France. The unity of the malady in the various lands is not fully established.

Etiology and Pathological Anatomy.—Ogata, in Japan, has described a protozoön parasite, which he names *Sporozoa muris*, as the cause of the malady. This organism he obtained from the blood and infected wounds of two cases. He was able to transmit it to rabbits and guinea-pigs and to cultivate it upon blood serum without loss of virulence. The author pictures an elaborate life-cycle, both sporozonic and schizogonic, with endocellular and free forms in the blood, glands, and viscera.

In the United States, Proescher has found a bacillus in the tissues about the wound of his patient, and in the organs of a guinea-pig, inoculated with the material. He was unable to cultivate the organism and transmit it to a second generation of guinea-pigs. Horder saw spirilla in one of his cases, while other observers have been unable to find any causative agent at all. The few autopsies on human cases have not disclosed any significant pathological changes, and apparently no one has identified or studied the infected rats.

In the tissue at the site of the wound there is lymphoid and connective-tissue hyperplasia, hyaline degeneration, and thickening of the blood-vessels.

Persons of all ages and both sexes are affected. There is some evidence for individual variation in susceptibility. The site of the wound does not seem to bear any special relation to the certainty or severity of the infection.

Symptoms and Course.—The bite wound usually heals spontaneously in a few days. After an incubation period of a few days to several months (average two weeks) there is a sudden onset with chill, fever, malaise, and sometimes joint pains. The temperature may reach 104° F., or higher. The fever persists for two to four days with remissions more or less marked, and falls suddenly to normal. During the febrile period there is headache, intense muscular pain, and often delirium.

[1] The most important articles are: Miyake, *Mitteil. a. d. Grenz. der Med. u. Chir.*, 1900, v, 231; Ogata, *Berlin. klin. Woch.*, 1908, xxxiv, 1099; Proescher, *International Clinics*, 1911, ser. XXI, iv, 77; Hata, *Münch. med. Woch.*, 1912, liv, 854; Horder, *Quarterly Jour. Med.*, 1910.

Coincident with the onset of the paroxysm, the bite wound becomes swollen, bluish red in color, and usually shows suppuration and necrosis later on. After sloughing, a circumscribed ulcer is left which heals rapidly.

The erythema is of the exudative type and appears in the first or later paroxysms and recurs with each exacerbation. The spots are seen on the extremities, face, and trunk, and vary from 0.5 to 5 cm. in diameter. They are slightly raised, bluish red, and not tender to touch. They fade slowly with desquamation and leave a stain in the skin which persists for some time. In addition severe transient urticaria is common toward the end of the disease.

The apyrexia lasts three or four days to two weeks, when another paroxysm is ushered in with chill, fever, and a fresh crop of erythematous spots. As the disease progresses, the febrile paroxysms tend to grow shorter. The periodicity of the fever varies, but is fairly constant for the individual case. The respiratory and circulatory systems are but little affected. Appetite is poor and there is often diarrhœa in the more severe cases. The liver and spleen are never enlarged in uncomplicated cases. Only such lymphatics as drain the area of the bite wound become swollen. A transient or permanent nephritis may develop with the severe cases. The blood shows a moderate leukocytosis.

The duration of the malady is a few weeks to many months, rarely a year or more. In addition to the classical type, there is an afebrile group with severe nervous symptoms, muscular palsies, coma, and death. An abortive type is also known, which ends favorably after one or two paroxysms. The mortality is estimated at 10 to 15 per cent.

Of the nervous features, delirium, coma, rarely twitching or convulsions, extensive paresis of the muscles of the extremities, anesthesia, and paresthetic skin areas may be found.

Diagnosis.—The cardinal features are: rat bite, intermittent fever, erythema of a bluish-red color, and muscular pain. Malaria is differentiated by the blood picture and enlarged spleen.

Prognosis.—The severity of onset, preponderance of nervous symptoms, and length of febrile paroxysms are important in determining the outcome. Marked œdema is of the gravest significance.

Treatment.—Free excision of the wound, even several weeks after the bite, supportive diet, and symptomatic therapy are indicated. Hata has reported 8 cases treated with salvarsan with good results.

PART III

NON-BACTERIAL FUNGUS INFECTIONS—THE MYCOSES

CHAPTER XXXIII

ACTINOMYCOSIS—STREPTOTHRICHOSIS—MYCETOMA—OÏDIOMYCOSIS—BLASTOMYCOSIS—SPOROTHRICOSIS—PULMONARY ASPERGILLOSIS—MYCOSIS—MUCORINA

By JAMES HOMER WRIGHT, A.M., M.D., Hon. S.D. (Harv.)

In this section are considered certain general and local diseases due to infection with fungi and certain branching filamentous microörganisms which are classed by some writers also among the fungi, but which may be regarded as representing intermediate forms between the bacteria and the fungi. Various local fungus diseases of the skin, such as favus, pityriasis versicolor, and erythrasma, known collectively as the dermatomycoses, are not included. Concerning the relationship and classification of the parasitic and pathogenic fungi, there is much uncertainty and lack of agreement among authorities.

ACTINOMYCOSIS

Actinomycosis is a suppurative process combined with growth of connective tissue and characterized by the presence in the lesions of vegetations or colonies of a specific microörganism, *Actinomyces bovis*. The disease may be local or general, subacute or chronic. It should be distinguished from so-called pseudotuberculosis or Streptothrix or Cladothrix infections or atypical actinomycosis. Such processes are considered under the name of Streptothrichosis.

Actinomycosis affects man and certain mammals, particularly cattle, in which it has been called "lump jaw," or "big jaw." The disease has a wide geographical distribution and is probably more common in man than is generally recognized. In cattle, bovine actinomycosis had long been known chiefly as a form of sarcoma of the jaw, when Bollinger, in 1877, first clearly showed that the disease was due to infec-

tion with a vegetable parasite, to which Harz gave the name of *Actinomyces bovis* on account of the radiate structure of its colonies or vegetations in the tissues. Shortly after this, J. Israel described cases in man, which we now know to be actinomycosis, and also described the characteristic microörganism, which he regarded as the infectious agent, but he did not recognize its identity with the microörganism described by Bollinger. The identity of the human and bovine disease was first pointed out by Ponfik.

Etiology.—The specific infectious agent exists in the lesions and in the pus in the form of small whitish, or yellowish, irregular shaped granules varying in diameter from a fraction of a mm. to 1 or 2 mm. Larger granules are usually made up of aggregations of smaller ones so that they present a mulberry-shape. The granules may be soft and easily crushed or hard, resistant, and even calcareous. The essential element of the granules is a branching filamentous microörganism and certain transformation and degeneration products thereof. Typically the granules present the following peculiarities of structure. Over more or less of the periphery of the granule are closely set, hyaline, refringent, club-shaped bodies of varying size and thickness arranged in a radiate manner, while elsewhere the periphery is occupied by filaments of the microörganism likewise closely set together and disposed in a radiate manner. All transitions between the filaments and the club-shaped bodies may be present. Beneath this peripheral layer of radiating club-shaped bodies and filaments is a dense net-work of branching interlacing filaments, while the central part of the granule may be occupied by necrotic and degenerate filaments and pus cells. The club-chaped bodies develop out of the peripheral filaments by the latter becoming invested with a sheath of hyaline refringent material which is usually thickest at or near the distal extremity of the filaments, and thus club-shaped bodies with filaments in the centre are produced. The "clubs" may attain a thickness many times that of the filaments, which may degenerate and disappear from within them. This sheath formation, may extend to the deeper lying filaments in the granule and these likewise may degenerate and become invisible so that the granule may finally be transformed into a mass of hyaline refringent substance and necrotic material, invested at the periphery with closely set radiating club-shaped bodies but without a trace of the filamentous microörganism out of which it was originally formed. In the "clubs," degenerate changes may occur whereby they acquire a lamellated structure or assume a varity of shapes and appearances. Eventually the granule may be absorbed or become calcified.

The "clubs," or rays, are usually better developed in the granules in bovine than in human lesions. In the latter they may be absent or poorly developed and the granules may consist entirely or chiefly of filaments. Certain cases in which the granules were destitute of "clubs" have been erroneously regarded as not being genuine actinomycosis and have been called pseudo-actinomycosis. This name has also been applied to certain suppurative conditions in which masses of various bacteria have been observed.

In general, the club formation is most marked in lesions in which there is considerable development of connective tissue and in which the progress of the disease is slow, with manifest resistance on the part of the tissue to the spread of the process; while in relatively rapidly progressive cases or those in which there is little evidence of resistance on the part of the tissue to the infection, "clubs" may be wanting on the granules. The writer[1] has shown that blood serum and serous pleuritic fluids are capable of provoking club formation by filaments in artificial growths of the microörganism that had been immersed in these fluids. From these facts and observations it seems probable that the club formation is a protective device, adopted by the microörganism to protect for a time the main mass of the microörganism constituting the granule from the destructive action of the tissue cells and juices.

Concerning the biology of the microörganism much confusion has existed and much that is erroneous has been written. Many workers have made culture experiments with very varying and often contradictory results. The subject has been further confused by classing with actinomycosis certain other suppurative processes due to infection with branching microörganisms which are widely different from the specific microörganism of actinomycosis.

The various branching microörganisms claimed to have been isolated in cultures from actinomycotic lesions, and to represent the microorganism of the lesions, may be roughly divided into two groups. All of these at some stage in their developmental cycle occur in filamentous forms, without sheaths or septa, and of a thickness of a medium-sized bacillus. They are distinguished from the bacteria by their peculiarity of truly branching, and may be regarded as occupying a position between the bacteria, on the one hand, and the hyphomycetes or mould fungi, on the other. One group is represented by the microörganisms described by Bostroem[2] and a few others; the other group, by the microörganisms of Wolff and Israel,[3] the writer, and many others.

The first mentioned group grow readily on all culture media, both at the room temperature and in the incubator. Their chief characteristic is the formation in cultures of spherical, spore-like, reproductive elements out of the substance of their filaments. None of this group are known to be capable of producing in animals inoculated with them, lesions like actinomycosis and containing the characteristic granules. The members of the other group do not grow on all the usual culture media and only feebly or not at all at room temperature. They do not form spore-like reproductive elements. Some of them have been shown to produce in animals inoculated with them lesions essentially identical with those of typical actinomycosis, although not of a progressive character.

It is the writer's opinion, based on his own observations and those of Shiota,[4] of Harbitz and Gröndahl,[5] and of others that only one species of microörganism, *Actinomyces bovis*, represents the specific infectious

[1] *Jour. Med. Research*, 1905, xiii, 349.
[2] *Beitr. z. path. anat. u. z. allgem. Path.*, 1891, ix, 1.
[3] *Virchow's Arch.*, 1891, cxxvi, ii.
[4] *Deutsch. Zeitschr. f. Chir.*, 1909, ci, 289.
[5] *Amer. Jour. Med. Sci.*, 1911, cxlii, 386.

agent of true actinomycosis in man and animals. This microörganism has properties essentially like those of the second group above mentioned. The microörganisms of the first group should not be considered as representing the microörganisms in the lesions, but are to be regarded as secondary invaders.

Concerning the mode of entrance of actinomyces into the tissues, it is generally believed that this microörganism is widely distributed in the outer world on grains and vegetable material and that it is carried into the tissues by penetrating foreign bodies of this kind, upon which it has its normal habitat. This idea is based on the following considerations:

The frequent occurrence of such foreign bodies in actinomycotic lesions; a history, in many cases, of the patient having taken uncooked grains or other vegetable material into the mouth; the occurrence of pulmonary actinomycosis in those who have breathed the dust of dried grains; the occurrence in the outer world, upon grains and grasses, of microörganisms with biological characters similar to, or identical with, those of the first group above mentioned—which Bostroem, Gasperini, and others claim to have isolated from actinomycotic lesions; the almost exclusive origin of actinomycotic lesions in the tissues and structures associated with the respiratory or alimentary tracts.

This widely accepted idea seems to the writer to be erroneous, because *Actinomyces bovis* does not have the biological characters of this saprophytic group assigned to it by Bostroem and a few others whose culture work is open to doubt, but has biological characters which suggest that it does not have its normal habitat outside the body where it has never been found under natural conditions. The writer believes that the specific microörganism of actinomycosis probably exists normally among the abundant flora of the secretions of the alimentary tract, where it has not been recognized because it exists there in a form which is not characteristic and very unlike that which it assumes in the lesions; it may gain entrance to the tissues through wounds, made by penetrating foreign bodies or otherwise, or through lesions due to carious teeth, or may invade the lungs and tissues as do other bacteria of the mouth and pharynx; in the tissues, under certain conditions it develops into the characteristic colonies or granules and by further proliferation gives rise to the disease. This hypothesis is supported by the fact that the disease in and about the jaws is frequently associated with carious teeth and by the observations of Lord,[1] who found that intraperitoneal inoculations of guinea-pigs with scrapings from carious teeth and from the tongue, and with material from the crypts of the tonsils, of persons free from actinomycosis, were followed by the formation of granulomatous nodules containing aggregations of branched, filamentous microörganisms with typical "club" formations and indistinguishable from the characteristic granules of *Actinomyces bovis*. That these microörganisms had the cultural peculiarities of the microörganism of actinomycosis could not be shown owing to technical difficulties and their identity with the latter is questionable.

[1] *Jour. Amer. Med. Assoc.*, 1910, lv, 1261.

Besides the specific and characteristic microörganism, various bacteria are also present in the lesions in many, if not most, cases of actinomycosis, and it seems very probable that these play an important part in the production of the disease in these cases.

Contagiousness has not been shown for actinomycosis. The small amount of evidence tending to show that it is contagious will not stand critical examination, and there is much direct evidence that it is not. Many experimenters have attempted to reproduce the disease by inoculating animals with material from actinomycotic lesions, but the results of most of them have been negative or ambiguous. Only a few report results that apparently constitute a true reproduction of the disease. In view of the low degree of virulence thus manifested by *Actinomyces bovis* in healthy experimental animals, it would seem that the occurrence of the natural disease must be due in large measure to the existence of an individual susceptibility. Thus it is most frequent in individuals living under unfavorable hygienic conditions. Infection from drinking milk and eating the flesh of diseased animals has never been proved.

It is claimed that more cases of the disease are found among persons living in cities and that it is more frequent in the months from August to January. It is more frequent in men than in women and in the middle decades of life.

Special Pathology.—The essential results are suppuration and tissue destruction, combined, in most cases, with new formation of granulation and connective tissue. In some cases the new formation of connective tissue may be excessive in amount, and thus simulate a neoplasm. The granulation tissue usually contains many large cells filled with fat globules. Giant cells may also be present.

The area of tissue affected by a given vegetation or colony is usually many times greater than the colony, the irritative action of the parasite affecting a wide area of the surrounding tissue. Almost any organ or part of the body may be the seat of the lesions. The extension of the actinomycotic process takes place both by continuity of the lesions and by metastases, the latter almost always occurring by the bloodvessels. In the lung the process may also be disseminated by way of the bronchi. The extension by continuity probably takes place by means of the separation from a colony of filaments and fragments of the microörganism. and the transportation of these in some unknown manner into the neighboring tissue, where they form new colonies and produce more foci of suppuration, tissue destruction, and inflammatory reaction. In this way large portions of an organ or region may become replaced by granulation and connective tissue, enclosing pus cavities; or large abscesses may be formed having the characters of cold abscesses. The small abscesses enclosed in the granulation and connective tissue often communicate with one another and may form sinuses discharging pus and inflammatory products. The small abscesses, with their associated connective tissue, may become very numerous and closely set together so that a focal lesion may arise, having the gross appearance of a sponge-like mass of connective tissue saturated with pus. This is typically seen in actinomycosis of the liver. A wide extension by continuity over

extensive areas and to distant portions of the body, and the formation of suppuration tracts and of sinuses, opening either on the skin or in mucous membranes, are marked features. The older lesions may heal by cicatrization and the dying out and absorption of the microörganism, so that the starting point of an extensive process may be difficult or impossible to find. Complete healing may occur spontaneously through the death and destruction of the microörganisms in the lesions and by its extrusion from the body by the way of sinuses or fistulæ.

Extension by metastasis takes place by the rupture of a focal lesion into a bloodvessel, thus discharging the parasite into the circulating blood, whereby the lesions may be widely disseminated throughout the body, affecting first the lungs, if a vein of the systemic system is involved, or the liver, if a vein in the portal system. Among many other possible localizations of metastatic lesions, the brain, the heart, and the extremities may be mentioned. In the heart the lesions may take the form of tumor-like masses projecting into its cavities from the walls. In these embolic disseminated cases, the process may have the character of multiple subacute abscess formation and thus be essentially a subacute pyemia. Extension by the lymphatics and involvement of lymphatic glands is very exceptional, if it occurs at all. In extensive chronic cases amyloid infiltration may occur. Carcinoma has developed in old lesions.

According to the point of origin or the principal location of the lesions, four forms of the diseases may be differentiated, viz., head and neck, thoracic, abdominal, and cutaneous.

Actinomycosis of the Head and Neck.—More than half of all the cases in man are of this form. It includes those in which are involved the structures in relation with the buccal and pharyngeal cavities, the tongue, the soft parts and the skin of the face and neck, the bones of the skull and jaws, the larynx, the thyroid, the lacrymal ducts and the brain. In these cases there may be extension to the meninges and brain through the skull or down the prevertebral space to the mediastinum and more distant parts. With the exception of the localizations in the lacrymal duct and in the brain by metastasis, it seems probable that the process in nearly all, if not all, cases of this form originates in the tissues immediately about the buccal and pharyngeal cavities. Cases in which this mode of origin is not obvious may be explained by the healing of earlier lesions. So-called primary cutaneous actinomycosis of the head or neck is open to question as to its origin in the skin in these situations. Lesions in the brain are usually metastatic. Only one case of apparently primary actinomycosis of the brain is known.

The muscular, bony, and other tissues may be extensively replaced by granulation and connective tissue enclosing suppurative foci, abscess cavities, and sinuses. The inflammatory tissue and infiltration may be excessive in amount, characteristically forming brawny indurations or sarcoma-like infiltrations and swellings in the parts affected. The skin over these may be œdematous, of a bluish or reddish color, and may present projecting folds or elevations with furrows between. Here and there points of suppuration, or the orifices of sinuses surrounded by red granulation tissue, may be apparent. In less extensive cases the inflam-

matory process may be insignificant and may heal spontaneously. Primary involvement of the jaw bones is rare. In the brain the lesions may be like abscesses or cystic cavities filled with a gelatinous grayish-yellow substance.

Thoracic Actinomycosis.—About 15 per cent. of all cases in man are of this form. In most cases the lungs are the seat of lesions which consist chiefly of abscess and cavity formation, usually combined with the growth of granulation and connective tissue at the expense of the pulmonary tissue, so that larger or smaller portions of the lungs may be transformed into fibrous tissue permeated with cavities and sinuses. The cavities, as a rule, are small. The inferior are more frequently affected than are the superior lobes. Lesions of the bronchi may be extensive. The rupture of a focal lesion into a bronchus often leads to dissemination of the process by way of the bronchial tree. The disease may originate in the bronchi, from the œsophagus, or from lesions involving the neck by extension downward into the mediastinum, or by extension upward from lesions in the abdomen, or by metastasis. From these situations the process may extend widely and involve the lungs and thoracic wall, producing retraction and deformity.

The initial and intermediate lesions in the evolution of the process may be healed and be neither obvious nor demonstrable. Cases of so-called primary cutaneous actinomycosis of the thorax probably represent an extension from within outward. The extension of the process through the wall of the thorax and the production on the exterior of the body of swollen and indurated areas in which are the orifices of sinuses, are characteristic features of this form of actinomycosis. These sinuses may open in the epigastrium as well as on the thorax.

In the pleural cavities an accumulation of serous fluid may occur, and empyema has been observed. The disease may extend from the mediastinum to involve the pericardium and heart. The lesions consist essentially in extensive replacement of the natural structures of the parts by inflammatory tissue in which are abscesses and sinuses.

Abdominal Actinomycosis.—About 20 per cent. of all cases in man are of this form. Any organ or region of the abdominal portion of the body may be affected and the lesions are very varied in character. The process may arise by extension from the thorax, by metastasis or by infection from the gastro-intestinal canal. It is probable that primary actinomycosis of the abdomen is always due to infection from the stomach or intestines and that the starting-point in these situations, when not demonstrable, has been a lesion that has healed. Primary lesions in the intestine appear as ulcerative processes.

The most frequent localization of the primary disease in the abdominal form is in the region of the cecum and vermiform appendix. From the intestine the disease usually extends—producing fibrous adhesions, suppurative foci and abscesses between intestinal coils—to the abdominal wall, most frequently in the right anterior half. Here the muscular and other tissues become replaced by inflammatory connective tissue in which are abscesses, sinuses, and intestinal fistulæ. The portions of the abdominal wall involved becomes brawny, and the amount of inflam-

matory connective tissue produced may give the appearance of a fibrous neoplasm. The skin over the affected region may be red, œdematous, and contain fluctuating suppurative foci, which by their rupture become the orifices of sinuses and fistulæ. Sometimes the process is circumscribed and a fibrous tumor-like mass attached to the intestine is produced.

Peritoneal abscesses may rupture into the intestine or bladder. From the abdominal wall the process may travel farther and produce extensive suppurating necrotic tracts, extending through the crural ring or along the psoas muscle to the hip-joint. The process may also spread from the intestinal canal along the retroperitoneal tissues, producing extensive destruction of the muscles and bone in this region, and eventually involve the thorax, or extend down into the ischiorectal fossa and perforate the skin in the region of the anus. Any of the abdominal or pelvic organs may become involved by direct extension of the process.

A frequent location of the lesions is in the liver, in which the foci may be single or multiple and are sometimes of large size. The lesions in the liver present the appearance of a sponge-work or honeycomb structure of connective tissue saturated with pus. They frequently arise from metastasis through the portal system as well as by direct extension. Cases of so-called primary actinomycosis of the liver have probably arisen by metastasis from healed or unrecognized lesions involving the portal system of veins. Metastatic lesions in abdominal actinomycosis arising from foci outside of the abdomen most frequently occur in the spleen, kidneys, and abdominal wall.

Cutaneous Actinomycosis.—This form includes those comparatively rare cases in which the lesions are regarded as primary in the skin. As already suggested, some of these cases represent secondary invasion of the skin from deeper structures. The lesions are ulcerative or may have great resemblance to lupus and to certain forms of cutaneous syphilis.

Symptoms.—In a disease with such a great variety of localizations and of such varying extent, it is impossible within the scope of this article to give an adequate account of all its signs and symptoms. These in general are like those of a subacute or chronic inflammatory process, or of a malignant neoplasm. In many cases the disease is far advanced and has extensively invaded important internal organs and regions before any symptoms are apparent.

In cases involving the external soft parts, prominent signs are swellings and indurations of the infected region in which suppurative foci, often recurrent, may develop, break through the skin, and become the orifices of recurrent sinuses and fistulæ. The skin over the affected part may be œdematous, discolored, and warm, or the swelling may have no inflammatory character and simulate a neoplasm. Fever and pain may or may not be present.

In the frequent cases in which the disease affects the temporomaxillary region the prominent symptoms are trismus, pain, swelling, and limitation of motion of the jaws. Involvement of the skin of the neck is characterized by ridge-like elevations, or folds with sulci between, associated with the orifices of sinuses. The lesions in the tongue are usually nodular or tumor-like.

Lesions of the brain, spinal cord, or meninges may give rise to all the various signs and symptoms of meningitis, encephalitis, myelitis, cerebral thrombosis, and tumor.

In those cases originating in any region of the body with extensive suppuration or with metastases, the symptoms are usually those of pyemia, with chills, sweats, fever, pain, vomiting, and diarrhœa. In such cases the primary process may not be obvious until the autopsy.

In the thoracic form definite symptoms and signs are usually wanting until the disease is far advanced. If the lungs are extensively involved there is cough with fetid, sometimes bloody sputum, and signs of bronchitis, pulmonary consolidation, and cavity formation. These usually are in the inferior portions of the lungs. There is also cachexia, anemia, fever of a variable type, and the habitus of pulmonary tuberculosis. The frequent involvement of the pleura and thoracic wall is a marked feature of this form of the disease and may give rise to the first symptoms. A prominent symptom of this localization is pain in the affected region. Retraction of the thoracic wall, signs of pleuritis, progressive emaciation, weakness, diarrhœa, night sweats, and fever may be present. The presence of an inflammatory swelling or a board-like induration in the wall of the thorax or epigastrium, with suppurative foci or sinuses in it, is very characteristic.

Lesions of the œsophagus have been attended with pain on swallowing or pain behind the sternum.

In primary abdominal actinomycosis the most conspicuous sign in the majority of cases is a deeply seated tumor-like mass or a hard infiltration, involving the abdominal wall, in the midst of which may be fluctuating foci or orifices or sinuses and intestinal fistulæ. The skin over the affected part may be red to brown in color and may be the seat of ulcers. Usually the affected region has a board-like consistence and is only slightly painful on pressure. The tumor-like masses are only slightly movable. The right half of the abdomen is most frequently involved, commonly in the ileocecal region. The left half is less frequently involved, while localization of the lesions about the umbilicus or in the lumbar or gluteal regions is rare. These local signs may or may not be preceded or accompanied by intestinal colic, vomiting, fever, diarrhœa, constipation, swelling of the abdomen, and pain referred to the ileocecal region or elsewhere.

The clinical course may be acute, with much fever and pain, as in the disseminated embolic forms, or it may be subacute or chronic, with little or no pain and fever. Any of the types may develop from one of the others. Fever may occur at any time. The spleen may be enlarged.

In the chronic cases especially there may be anemia, diarrhœa, emaciation, weakness, œdema, and cachexia. Ascites rarely occurs. In cases in which the liver is extensively involved the organ is enlarged, but there may be little fever and but little pain referred to it. Pain in the lower ribs, jaundice, and constipation may be present. An abscess may be evident in the right hypochondrium, and there is the fever curve of suppuration. Sometimes there is a painless tumor at the right

costal border, with only moderate fever. Involvement of the urinary tract may produce symptoms of cystitis and pyelonephritis.

Diagnosis.—So closely does actinomycosis simulate various inflammatory conditions and tumor formations that the diagnosis is definitely established only by the demonstration of the characteristic microörganism in the lesions, or in the pus aspirated or discharged from them. The characteristic granules are rather to be sought for in the pus or discharges from the lesions than in pieces of excised tissue, because the granules or vegetations commonly exist in little cavities or sinuses in the tissue, from which they readily escape and are lost, or in which they may be concealed and elude observation owing to the small size of the granule as compared with the mass of the lesion.

The pus or the sputum, in cases of suspected pulmonary actinomycosis, should be spread out thinly on a glass surface and the granules sought for against a dark background. A careful examination may be necessary to find them. Suspected granules should be transferred to a slide, with a small amount of water, and gently flattened under a cover-glass. Under the microscope with a low power objective a typical granule appears as a brownish refringent, more or less lobulated mass or masses showing radiate striated appearances at the periphery. More or less pus adheres to the granule, so that the masses of the parasite are seen to be surrounded by pus cells. Under an objective of medium magnifying power the peripheral portions of the granule are seen to be composed of the characteristic refringent radiating club-shaped bodies or filaments closely packed together and the central portions are seen to be granular or hyaline. In some instances the clubs may not be present and filaments only may be apparent at the margin.

Granules composed of conglomerates of various bacteria, such as may be observed in pus from inflammatory processes about the mouth, should not be mistaken for granules or colonies of actinomyces. If the granules do not show the "clubs," the demonstration in smear preparations made from them of truly branched filaments, like those of actinomyces, is sufficient to justifiy the diagnosis of actinomycosis. This is best done by breaking up one or more of the granules on a cover-glass so as to form a smear preparation, staining it by Gram's method and examining with an oil-immersion objective. In addition to longer and shorter irregularly staining filaments, often branched and occurring singly or in groups or in masses, coccus-like or bacillus-like forms may be seen. These are either products of disintegration and generation of the filaments of actinomyces or are true micrococci and bacilli that have been growing in symbiosis with them. The coccus-like forms have been erroneously regarded by some writers as spore-like reproductive elements of actinomyces.

The pus of closed suppurative foci is most favorable for the finding of the microörganism, and the first drops of pus or inflammatory fluid which issue from the focus are best to examine, for the granules are usually most numerous therein. They may be very few and difficult to find in the inflammatory fluid that may be expressed later from the lesions. The secretions from open sinuses may be very poor in granules,

and, in suspected cases with sinus formation, it may be necessary to examine the secretion accumulated during some time.

The existence of subacute or chronic indurated swellings, associated with recurrent suppurative foci or sinuses or fistulæ in any situation, is suggestive of actinomycosis.

Actinomycosis of the neck and head may be confounded with any of the tumors or inflammatory conditions occurring in these parts, especially with sarcoma of the jaw. In every inflammatory process about the mouth or pharynx actinomycosis should be considered. Actinomycosis of the tongue may be confused with cancer and other conditions. Actinomycosis of the brain may be suspected only when cerebral symptoms occur in association with a focus of known actinomycosis elsewhere. Actinomycosis of the thorax may simulate every inflammatory or neoplastic affection of that part of the body.

In cases involving the lung without obvious lesions of the thoracic wall, the disease is most likely to be confused with pulmonary tuberculosis, from which it differs clinically practically only in the more frequent localizations of the signs in the inferior lobes and in the less frequent occurrence of hemoptysis. In these cases the diagnosis can be made with certainty only by finding the characteristic granules or colonies of actinomyces in the sputum or in the pleural exudate. The sputum in all cases of chronic pulmonary disease in which tubercle bacilli cannot be found should be examined for actinomyces. The granules usually sink to the bottom of the sputum receptacle. Any concretions in the sputum should be carefully examined. *X*-ray examination may be of service in diagnosis for the inflammatory tissue of the lesions may produce intense shadows.

The early symptoms may be those of typhoid fever or influenza accompanied by pleuritis, and the persistent pulmonary symptoms may be regarded as sequelæ of these affections. In cases in which the thoracic wall or vertebral column is involved the disease may simulate chiefly tuberculosis or secondary carcinoma of the spine, or sarcoma or cold abscess of the thoracic wall.

Involvement of the œsophagus may simulate cancer of that organ.

Abdominal actinomycosis may simulate a great variety of diseases and conditions, among which may be mentioned tumors, gumma, and phlegmon of the abdominal wall, appendicitis, typhoid fever, carcinoma of the intestines, tuberculosis of the ileocecal lymph nodes, abscess of the liver, psoas abscess, perinephric abscess, and sarcoma of the iliac bone. If neither superficial suppurative foci, nor sinuses, nor fistulæ exist, it is possible that the actinomyces granules might be found in the feces or in the urine, if the intestine or bladder be involved.

Prognosis.—The prognosis depends chiefly upon the extent and localization of the lesions. In nearly all cases the disease is chronic, lasting for months and years. Some cases recover spontaneously, but for the great majority treatment is necessary to make recovery possible.

In cases affecting the head and neck the general prognosis is much better than in the other forms. Maier[1] has analyzed the results reported

[1] *Beitr. z. klin. Chir.*, 1909, lxiii, 472.

in 177 cases under various forms of treatment. Of these 152 or about 85 per cent. were regarded as cured with more or less probability. When the disease involves the superior maxilla and the pharynx the prognosis is not as good as in the generality of the cases of the head and neck.

Recurrences are not infrequent after operation or apparent cure, and a case should not be regarded as cured until two years have elapsed without recurrence.

The prognosis in the thoracic form is bad. As in nearly all of the cases of the thoracic form the lung is involved, statistics bearing upon prognosis in this form deal chiefly with pulmonary actinomycosis. Among 58 cases collected by Illich,[1] no recoveries are recorded. Maier found that only 7 of the 35 cases in the literature analyzed by him apparently recovered under treatment.

In abdominal actinomycosis the prognosis is not good, but it is better than in the thoracic form. It is especially bad if the retroperitoneal tissues are involved. It is better if the process is localized in the anterior abdominal wall, is accessible to surgical treatment, and the visceral involvement is lacking or not extensive. Of 107 cases reported by Grill,[2] of which 77 were treated surgically, 22 recovered and 45 died. Löwe[3] selected 67 cases in which the disease was localized about the ileocecal region and found that 12 recovered and 36 died. Of the 59 treated cases analyzed by Maier, 30 were considered to have been cured. At least 1 case of spontaneous recovery is known.

Treatment.—The weight of experience is in favor of surgical means combined with the internal administration of large doses of iodide of potassium continued over long periods of time. The favorable effect of this drug in many cases seems to be generally admitted. It is said to cause more or less absorption of suppurative foci and to facilitate the discharge of the specific infectious agent from the tissues. It seems also to inhibit the development of new suppurative foci. Cures are claimed to have been effected by the use of this drug alone. It is said to act less favorably in pulmonary actinomycosis than in other forms. It must be given in the largest doses that can be borne. Favorable effects may not be apparent in the lesions until its administration has been continued for a considerable length of time. Maier prefers sodium to potassium iodide on account of the toxic effects of the latter salt upon the heart. He reports cures in 18 out of a series of 23 cases affecting the head and neck by the administration of the iodides internally combined in most instances with incision and tamponades. Treatment with the *x*-rays combined with the internal administration of large doses of potassium iodide has been highly recommended.

Opinion is divided as to the character of the surgical treatment. Some advocate the radical excision of the diseased tissue when the character of the case admits of it. This seems to be the only effective treatment in the thoracic form of the disease, but is only applicable to

[1] *Beitr. z. Klinik der Aktinomucose*, 1892, Wien.
[2] *Beitr. z. klin. Chir.*, 1895, xiii, 551.
[3] "Statistisches und Klinisches zur Kentniss der Actinomycose des Wurmfortsatzes und des Cöcums," *Inaug. Diss.*, Greifswald, 1904.

rare cases in which the process is localized. Others believe that wide opening and drainage of abscesses, sinuses, and fistulæ, with or without thorough curetting, is sufficient. With the latter mode of treatment tamponades of iodide of potassium and of various antiseptics have been advocated, such as tincture of iodine, corrosive sublimate, sulphate of copper, and nitrate of silver. In localization about the jaw, any carious teeth in relation with the lesions should be extracted. For rectal actinomycosis, Poncet recommended the thermocautery.

Recurrence is frequent, so that repeated operation may be necessary before a cure is effected. As a prophylactic against recurrence a course of treatment with iodide of potassium is advocated. This has also been advised as a preliminary to surgical treatment in cases with extensive lesions, as in abdominal actinomycosis, because its effects on the lesions tend to make the suppurative foci more evident, and thus more easily found and evacuated by operation. The internal administration of arsenic and of sulphate of copper has also been advised.

V. Baracz[1] recommends in circumscribed lesions, especially those about the face and neck, where it is desirable to avoid cicatrices for cosmetic reasons, the parenchymatous injection of tincture of iodine, or of a 20 per cent. solution of nitrate of silver without extensive surgical interference, 1 cc. or 16 minims of either of these to be injected into the lesions repeatedly every few days. One case of pulmonary actinomycosis is claimed to have recovered under treatment with oil of eucalyptus. According to v. Baracz the surgical treatment of pulmonary actinomycosis has not given hopeful results.

Treatment by the subcutaneous injection of killed cultures of the microörganisms has not been tried on a sufficient number of cases to justify an opinion of its value.

STREPTOTHRICHOSIS

Definition.—A considerable number of cases of inflammatory character, due to infection with branched filamentous microörganisms more or less similar to *Actinomycosis bovis*, are recorded in the literature and have been the source of much confusion. A few of these cases are infections with branched tubercle bacilli or are cases of pulmonary gangrene associated with so-called branched bacilli, the pathogenic significance of which is doubtful; these need not be further considered here.

Excluding a few cases, which are more or less probably genuine actinomycosis, in which the infecting microörganism had not developed the characteristic "clubs," and some cases that are very meagerly reported, a considerable group of cases remains which either have been shown, or may at present be assumed, to be cases of infection with different species of a single genus of microörganisms, the chief characters of which are described below. To the cases in this group the terms pseudotuberculosis, or *Streptothrix*, or *Cladothrix* infection, or atypical

[1] *Arch. f. klin. Chir.*, 1902, lxviii, 1050.

actinomycosis have been applied. None of these names is satisfactory. Pseudotuberculosis is too indefinite a term and carries no etiological suggestion. *Streptothrix* and *Cladothrix* are generic terms that, according to the rules of botanical nomenclature, are untenable for the group of infecting microörganisms in question, for they have been used as generic names for microörganisms quite different from these. Atypical actinomycosis is objectionable, because it leads to the confusion of these cases with actinomycosis and because it implies that the infection microorganism is so closely related to *Actinomyces bovis* as to be classed in the same genus with it.

This idea of the close relationship of the infecting microörganism in these cases to *Actinomyces bovis* is widely accepted, but the writer[1] has shown that it is erroneous and that *Actinomyces bovis* differs so markedly from the microörganisms of this group that it should not be placed in the same genus with them. In spite of the objection noted above to the name *Streptothrix* as applied to these microörganisms, infections with them continue to be called Streptothrichosis, and these terms seem now to be widely accepted and justified by usage.

Etiology.—The infecting microörganisms in streptothrichosis have resemblances, on the one hand, to certain bacteria in the structure, thickness, and staining of their filaments, and, on the other hand, to the hyphomycetes or moulds in their branching, thread-like form and in the production of fine conidia or spore-like reproductive elements out of the substance of the filaments. They differ from the hyphomycetes in that their filaments are more slender and are not tubular structures with double contoured walls, protoplasmic contents, and transverse septa. They may be regarded as representing a further transition from the bacteria toward the lower fungi or hyphomycetes than does *Actinomyces bovis*, because they have this property of producing spore-like reproductive elements or conidia, a property not possessed by that microörganism.

Most of the known species grow readily on the ordinary culture media are aërobic and do not require the temperature of the body for their multiplication. They grow in dense masses on culture media, on which the younger colonies may appear as aggregations of filaments radiately arranged. They are widely distributed in the outer world, especially in the air and on grains and grasses. The various species differ chiefly in the color and appearances of their growths on artificial media.

It is very probable that the streptothrices, claimed to have been isolated from certain cases of inflammatory lesions as well as from certain cases of typical actinomycosis, gained entrance to the culture tubes by accident or were secondary invaders of the lesions.

Infection seems to take place most frequently through the respiratory tract. In four cases it has occurred from wounds. Malnutrition and chronic disease seem to predispose the individual to this infection. Including four animal cases, there are at least twenty-seven well authenticated cases of infection with *Streptothrix* from which the microörganism

[1] *Journal of Medical Research*, 1905, xiii, 349.

has been isolated and studied in pure culture. In a smaller number of cases regarded as such, culture experiments have not been successful or were not attempted. The organisms isolated in the cultures have shown sufficient differences among themselves to be regarded as belonging to various species.

Analysis of the better studied cases shows that the microörganisms from at least fifteen of the human cases and from one case in a dog were sufficiently alike to be considered as probably belonging to the species first described by Eppinger, who gave it the specific name of "asteroides" and the untenable generic name of *Cladothrix*. This species is characterized by the reddish color of its growths on culture media, by not liquefying gelatin and by producing so-called pseudotuberculosis in animals inoculated with it. The lesions in these animals consist of foci of suppuration surrounded in typical instances by more or less well-developed granulation tissue. They may be very extensive and widely disseminated throughout the body. A marked peculiarity of most of the microörganisms concerned in streptothrichosis is their resistance to decolorization by weak acids after being stained by fuchsin.

The wide distribution of the streptothrices in the outer world has already been referred to, and it seems very probable, in view of the biological characters of those that have been isolated from pathogenic processes, that they likewise have a natural habitat outside of the body.

Special Pathology.—The lesions are of varied character and these microörganisms produce necrosis, suppuration, abscesses, and granulation-tissue formation as well as miliary focal lesions that are essentially suppurative foci surrounded by more or less granulation tissue, but it is not proved that fibrous or calcareous nodules, areas of caseation and tubercles identical in structure with those of tuberculosis, can be produced by them. The filaments of the infecting microörganism are scattered among the cells of the lesions or are loosely grouped together, and are not aggregated so as to form the compact masses or radiate structures or granules that are characteristic of actinomycosis.

The process in most of the cases has been situated in the lung or has originated there. In the lungs pneumonia, abscesses, gangrene, indurative processes, fibrous nodules, cavities, caseous pneumonia, miliary tubercles, and other lesions like those of tuberculosis, have been described. It is uncertain whether these lesions, like those of tuberculosis, are due to the *Streptothrix* rather than to the tubercle bacillus. In two cases the reporters considered tuberculosis to be coincident.

Metastatic lesions have been observed in at least 11 cases, among which the brain, myocardium, lung, kidney, spleen, peritoneum, lymphatic glands, and subcutaneous tissue have been involved. The primary process was in the lung in 7 of these cases; in a bronchial gland in 1 or 2; in the region of the knee-joint in 1; and was unknown in 1. In 8 cases there were 1 or more abscesses in the brain. In 2 cases there was empyema and pericarditis. One case was of the nature of a subacute purulent peritonitis, and another of the nature of a general infection with repeated growth of the microörganism in cultures from the blood during life.

Conjunctivitis and subcutaneous abscess have also been ascribed to infection with Streptothrix. In the animal cases there was suppuration in various regions.

Symptoms.—The symptoms are in general those of suppuration or inflammation and have varied with the location and extent of the process. The clinical course was either acute or chronic. In most of the pulmonary cases the signs and symptoms have been those of pulmonary tuberculosis or of pneumonia and abscess. Cough, fever, pain, and emaciation have been observed. In 2 cases there was hemoptysis. Signs of empyema were present in 2 cases, in one of which there was an inflammatory fluctuating tumor on the external aspect of the chest wall. In 1 of these cases also signs of pericarditis were made out. In 2 cases there were multiple metastatic abscesses in the subcutaneous tissue with symptoms of pyemia. In 1 of these infection with the bacillus of glanders was suspected. In a few cases the process has been essentially of the character of a terminal infection. In 3 of the cases in which there was abscess formation in the brain, there were symptoms of tumor and abscess in 2, while in 1 the diagnosis of tuberculous meningitis was made. In the case of subacute peritonitis which followed gastrotomy, the prominent symptom was diarrhœa.

Diagnosis.—Streptothrichosis may be confused with a variety of diseases, but especially with pulmonary tuberculosis and actinomycosis. In cases with multiple abscess formation in the subcutaneous tissue the disease may simulate infection with the bacillus of glanders. The diagnosis depends upon finding the special microörganism in the sputum or in the lesions. It occurs typically in the form of branched filaments of the character above described, which resist decolorization by dilute acids after having been stained with fuchsin. Fragments of the Streptothrix may be mistaken for tubercle bacilli, especially for the rare branched forms of that microörganism.

The Streptothrix may be distinguished from the tubercle bacillus by its longer filaments and more marked branching and also by its occurrence in loose aggregations. A further distinction lies in the fact that most of the streptothrices after staining with fuchsin do not resist decolorization with acids as strongly as the tubercle bacillus, and are decolorized by alcohol, whereas the tubercle bacillus is not. Probably the best way of finding them in sputum or pus is by the microscopic examination of smear preparations stained by Gabbet's method, for this does not employ alcohol and is not a very vigorous discolorizer.

The streptothrices are distinguished from the microörganism of actinomycosis in that they do not occur in the inflammatory fluids or lesions in man in the compact masses nor form the radiate club-bearing structures or granules so characteristic of actinomycosis. Moreover, the microörganism of actinomycosis does not resist decolorization by dilute acids after having been stained with fuchsin. Localization of the lesions about the mouth and jaws, so common in actinomycosis, is unknown in streptothricosis.

Prognosis.—All of the patients in whom the lung or brain was involved died except two, who got much better or recovered. These two cases

were among the less well authenticated ones. One case, in which the microörganism was apparently present in the circulating blood, recovered.

Treatment.—No specific is known and the treatment will vary with the character of the process and the situation of the lesions. In cases resembling pulmonary tuberculosis the treatment is essentially the same as for that disease. Empyema and abscesses should be treated according to the usual surgical principles.

MYCETOMA (MADURA FOOT)

Definition.—Mycetoma is a chronic infectious process, most commonly affecting the foot, the prominent features of which are multiple sinuses and enlargement and distortion of the parts. Carter[1] first assigned to the disease a separate identity and a special parasitic causation.

Etiology.—The affection is characterized by the presence, in the diseased tissue and in the discharges from sinuses, of peculiar granules usually not more than 1 mm. in diameter but sometimes larger. In certain cases these granules are of black color, of irregular shape, hard, rather brittle, and, in general, resemble grains of gunpowder. In other cases the granules are whitish, grayish or yellowish in color, of a soft or cheesy consistence, and have been compared to fish roe in appearance. A few cases are recorded in which the granules were of a red color.

The granules are composed of aggregations of vegetable parasites and their products. On account of their relation to the lesions the granules are presumed to be the cause of the disease and not merely secondary invaders. Two varieties or forms of the disease are recognized: the "melanoid" or black variety, in which the granules are black, and the "ochroid" or pale variety, in which the granules are white to yellow.

The ochroid granules in some cases are apparently identical with the granules of actinomyces. Our knowledge of the cultural peculiarities of the parasites is very meager. Musgrave and Clegg[2] cultivated a streptothrix from a single case and produced the disease in the monkey by inoculation.

The black or melanoid granules, as shown by the studies of Bristowe, Carter, Wright,[3] and others, are of entirely different character. They consist of a mass of hyaline refringent, brown-colored, brittle substance, forming a matrix in which are imbedded a tangle of fungus tubules or hyphæ with doubly contoured walls and transverse septa. This fungus of the melanoid form of the disease has been isolated in cultures by the writer from a single case. It has the characters of a white mould or hyphomycete without spore formation.

Chatterjee[4] reports a case in which the granules consisted of black-tinted mycelial threads without imbedding matrix. His cultures developed a hyphomycete which differed from the one isolated by the writer. Brault[5] also reports the cultivation of a hyphomycete.

[1] A. V. Carter: *On Mycetoma or the Fungus Disease of India*, London, 1874.
[2] *Philippine Jour. of Sci.*, 1907, ii, 477.
[3] *Journal of Experimental Medicine*, 1898, iii, 421.
[4] *Centralbl. f. Bakteriol.*, 1 Abt., Jena, 1912, lxi, 358.
[5] *Arch. de Parasitol.*, 1911–12, xv, 218.

The mode of entrance of the parasite into the tissues is not known. The disease is endemic in certain districts in India, especially in Madura, and has been observed in Africa, Italy, and other tropical or subtropical countries. It seems to be acquired in the country districts and not in towns. In America it is of very rare occurrence, only five undoubted cases having been reported, and four of these were of the pale variety of the disease.

Special Pathology.—The process consists essentially in abscess and sinus formation, associated with extensive development of granulation and connective tissue. The granules are found in the abscesses or sinuses, and sometimes they may be found surrounded by epithelioid cells and giant cells. Giant cells may be frequent in the granulation tissue. The inflammatory tissue may very extensively replace the muscles and bones of the affected part, the tendons and fascia most resisting replacement. In advanced cases the granules may exist in sinus cavities in masses. The foot is most commonly affected, but occasionally the hand and, rarely, other parts. The internal organs are never involved.

Symptoms.—The process usually begins as a firm nodular swelling in the sole of the foot, which is followed by others in the neighborhood or elsewhere. These break down and become the seat of the openings of sinuses which rarely heal. By extension of the process the foot increases in breadth and thickness and may attain a considerable bulk and weight, eventually becoming very burdensome to the patient. The toes become more or less displaced and deformed. The orifices of sinuses may be obscured by masses of granulation tissue. The discharges from the sinuses are oily, mucopurulent, and may have a very bad color. They contain the characteristic granules above described. Severe pain is rare. In advanced cases the great weight of the foot prevents its use in walking, and atrophy of the leg muscles occurs.

Diagnosis.—The disease may be mistaken for syphilis or for sarcoma. The diagnosis depends upon finding the granules and upon recognizing their characteristic structure. To cases of the pale or ochroid variety, what has been written upon the diagnosis of actinomycosis applies. The fungus elements in the black granules are best demonstrated by softening and bleaching the granules with liquor sodæ chlorati and examining teased preparations under the microscope. In such preparations the fungus elements should be clearly visible as septate, tubular, cylindrical, or spherical structures with doubly contoured walls.

Prognosis.—The process is very chronic and may last for years. Spontaneous recovery never occurs. Death may follow from secondary infection with pyogenic microörganisms or may be due to exhaustion.

Treatment.—The internal administration of iodide of potassium is said to have no favorable effect upon the process. The only effective treatment is excision of the lesions or amputation.

OÏDIOMYCOSIS

Definition.—A granulomatous and suppurative process affecting the skin and internal organs. It is called dermatitis coccidioïdes, protozoic

dermatitis, blastomycetic dermatitis, coccidioïdal granuloma, and blastomycosis. More than 140 cases have been reported. The first cases were described by Wernicke,[1] Busse,[2] and Gilchrist and Stokes.[3] Good descriptions of the disease with summaries of collected cases have been published by Montgomery and Ormsby[4] and by Hektoen.[5]

Etiology.—The disease is due to infection with certain fungi which may, according to Ricketts,[6] be classed as species of the genus *Oïdium*. In the lesions the microörganisms appear chiefly as spherical bodies, each consisting of a protoplasmic mass enclosed in a doubly contoured hyaline capsule, which may be provided with prickles or spines in some instances. The diameter of the bodies varies up to thirty microns or more. In the protoplasm, vacuoles, granules, and various markings may be seen, but no nucleus is apparent. The mode of proliferation in the lesions in the majority of cases is by gemmation or budding. The microörganisms in some cases have great resemblance to yeast fungi or saccharomyces. Busse regarded the microörganism in his case as a yeast and called the process saccharomycosis. In a minority of the known cases, proliferation of the microörganisms in the lesions is not by budding but by a process which is regarded as one of sporulation, the protoplasm of the larger forms segmenting into many small spherical bodies. Each of these small spherical bodies acquires a capsule and, being set free by the rupture of the capsule of the mother cell, develops into the adult parasite.

Wernicke, and Rixford and Gilchrist,[7] first described cases with these sporulating forms in the lesions and they regarded the microörganisms as protozoa; but later Ophüls and Moffitt[8] showed that they are stages in the life-cycle of a mould fungus. The microörganisms may be few or very numerous in the lesions. In cultures the microörganisms show considerable variation in biological character.

According to Ricketts, the microörganisms obtained from various cases may be divided into three groups, according to their biological characters, as shown in the cultures as follows:

1. Those growing chiefly as spherical or oval budding cells and resembling yeasts, but capable of producing mycelium.
2. Those forming submerged mycelium, which breaks up into chains of spores, while proliferation by budding is not a prominent feature.
3. Those producing mycelium with fruit-bearing aërial hyphæ and also capable of multiplying by gemmation or budding.

The microörganisms of the first and second groups are capable of producing fermentation, while those of the third group are not. In animals inoculated with cultures of some, but not all, of these microorganisms, abscesses, granulomatous tumors, and tubercle-like nodules

[1] *Centralbl. f. Bakteriol.*, 1892, xii, 859.
[2] Ibid., 1894, xvi, 175.
[3] *Bulletin of the Johns Hopkins Hospital*, 1896, vii, 129.
[4] *Arch. of Int. Med.*, 1908, ii, 1.
[5] *Jour. Am. Med. Assoc.*, 1907, xlix, 1071.
[6] *Jour. Med. Research*, 1901, vol. vi.
[7] *Johns Hopkins Hospital Reports*, 1896, i, 209.
[8] *Philadelphia Medical Journal*, June 30, 1900.

widely disseminated have been produced. In these lesions in the animals the microörganisms exist in the same form as in the human lesions.

Wolbach,[1] working with a microörganism of the type which proliferates in the tissues by sporulation, has studied carefully, in animals inoculated with pure cultures, the transformation of the hyphæ of the cultures into the characteristic spherical bodies of the lesions. He finds that the spherical bodies arise by the segments of the hyphæ enlarging and assuming a spherical shape, the wall of the segment thus becoming the capsule of the spherical body. In his experimental lesions Wolbach has also observed pointed and club-shaped hyaline bodies radiately arranged continuous with the capsules of the microörganisms.

The conditions underlying infection in oïdiomycosis are not yet known. There is no definite relation between the disease and age, occupation, nativity, or habits of the patients. Males have been more frequently affected than females. Most of the cases with so-called sporulating forms in the lesions have occurred in California, while most of the cases with budding forms have occurred in Chicago or its vicinity. There is no good evidence that the disease is hereditary or that it is contagious. A few cases followed traumatism.

Special Pathology.—The process usually consists in abscess formation, combined with proliferation of the fixed cells of the infected region; but in cases of infection with the sporulating form of the parasite, it may be characterized by the formation of caseating aggregations of epithelioid cells accompanied by giant cells, thus simulating tuberculosis. The reaction on the part of the tissue in some cases may be comparatively slight and the lesions may consist chiefly of masses of the microörganisms. Multinucleated giant cells containing the parasites are prominent features of the lesions. In the skin there may be extensive hyperplasia of the rete mucosum, abscesses both in the corium and in the rete, and tubercle-like aggregations of epithelial cells with giant cells. The microscopic appearances may simulate squamous-cell carcinoma or verrucose tuberculosis and the microörganism may be present in comparatively small numbers. The lesions may be limited to the skin or may involve also the lungs and internal organs. The disease may take origin in the lungs. The face is most frequently the seat of cutaneous lesions, but the skin of almost any region of the body may be involved.

The skin involvement may be very extensive. There is but little tendency to involve mucous membranes. The cutaneous lesions usually occur as papules or pustules, or as cutaneous nodes which in the course of days or weeks enlarge and form abscesses containing a glairy mucopus. These abscesses commonly give rise to ulcers which may become covered with bulky crusts or assume verrucose, fungoid or papillomatous appearances by the growth of granulation tissue in which small abscesses may develop. Sometimes the cutaneous lesions take the form of larger and smaller elevated patches with rough, scaly, irregular, or papillomatous surface, enclosing numbers of minute abscesses. These patches may also ulcerate. In the older lesions and parts of progressive lesions,

[1] *Jour. Med. Research*, 1904, xiii, 53.

cicatrization may occur. Large abscesses involving the deeper tissues may also form. In many cases the cutaneous lesions are multiple and they may be situated in widely separated parts of the body. They may appear in successive crops. In one case 93 cutaneous lesions were present.

Involvement of other organs and structures, not cutaneous, has been observed in more than 40 cases, only in a few of which cutaneous lesions were absent. Among these cases the lungs, pleura, heart, liver, kidneys, spleen, pancreas, bones, joints, suprarenals, testicles, prostate, vermiform appendix, peritoneum meninges, brain, and various lymphatic glands have been the seat of lesions. In the lungs, which were the organs most frequently affected, the lesions have consisted of abscesses, miliary nodules, bronchopneumonia, and areas of consolidation. In the other organs the lesions have consisted of small nodules, abscesses, cheesy, or necrotic areas or grayish-white infiltrations. When the process has involved the bones it has been suppurative and necrotic in character, sometimes simulating tuberculosis. Psoas, perinephric, abdominal, thoracic, and retropharyngeal abscesses have been noted. Lesions of lymph nodes are more frequent in infections with the sporulating form of the parasite. Amyloid infiltration has been observed.

Symptoms.—In most of the cases the disease is very chronic, lasting for years. The cutaneous lesions in most cases have periods of rapid progression interrupted by periods of relative quiescence. They may exist for years without involvement of the internal organs. There may be severe pain. In cases involving the lungs and other internal organs, the symptoms and signs are very similar to those of tuberculosis or of pyemia. Prominent symptoms are cough, discomfort in the chest, expectoration, sometimes blood-stained, and fever, highest at night. Sweating has been observed in these cases. Eventually there is emaciation and asthenia. The pulmonary lesions do not as a rule give marked physical signs. In some cases febrile pulmonary disturbances have preceded the appearances of the cutaneous lesions or new crops of lesions. Gastro-intestinal disturbances, chiefly in the form of diarrhœa, have been noted in several cases.

Diagnosis.—The cutaneous lesions are most likely to be confounded with verrucose tuberculosis, but they may also resemble carcinoma, mycosis fungoides, as well as certain forms of syphilis of the skin. The diagnosis can only be made with certainty by finding the microörganism in the lesions. This is best done by examining the contents of the small abscesses or a fragment of the tissue with the microscope and finding the fungus cells. A drop of the pus mixed with water or a 10 per cent. sodium hydrate solution may be placed under a cover-glass and examined directly without staining. The cases in which the lungs are involved may be regarded as pulmonary tuberculosis. The diagnosis in such cases will depend upon the recognition of the nature of any coexistent cutaneous lesions, or it may be made by finding the fungus in the sputum, where it has been demonstrated in 6 cases. The fungus has been demonstrated in the cerebrospinal fluid in a case of meningeal involvement and in the urine in a case of abscess of the prostate. It has also been

observed in the feces. In one case it was obtained in a culture from the blood during life.

Prognosis.—When the disease is primary in the skin it is generally very chronic and may persist for ten years or longer. Cases infected with the sporulating form of the parasite are more frequently fatal than those infected with the budding forms.

When confined to the skin the disease yields to proper treatment, with a varying amount of cicatricial deformity. Spontaneous healing may occur, at least in some of the lesions. After the lungs and other viscera have become extensively involved the disease may terminate fatally within a few months. Of the 22 cases of this kind analyzed by Montgomery and Ormsby, only 2 were believed to have recovered while 17 were known to be dead.

Treatment.—The internal administration of iodide of potassium have been employed with considerable success in the localized cutaneous forms. It should be given in large doses; 50 to 150 grains (3.75 to 10 gm.) have been given three times daily. This may be combined with treatment by the *x*-ray, especially in the superficial cases. Simple local antiseptic treatment of the cutaneous lesions has not given good results. It is of value in relieving soreness and preventing secondary infections, as well as in cleansing the lesions. Total excision when the lesions are limited gives the best results. Thorough curetting followed by cauterization has been advised. There is some evidence, however, that curetting may lead to general dissemination. Walker and Montgomery[1] recommend the actual cautery or free excision, with deep dissection and repairs by skin-grafts or plastic operations, in those cases in which iodide of potassium fails to cure. They do not recommend curetting. Sulphate of copper administered internally in doses of from one-fourth to one grain three times daily and applied externally as a wash in 1 per cent. solution has been employed by Bevan.[2]

The treatment of cases in which the disease is widespread and the internal organs involved is very unsatisfactory. The only hope seems to be in the administration of large doses of iodide of potassium combined with measures which tend to improve the general nutrition and resistance.

Addendum.—Closely allied to the microörganisms of oïdiomycosis is the microörganism of parasitic stomatitis or thrush—the *Oïdium albicans*. In a very few cases this *Oïdium* has invaded internal organs and has been found in abscesses in the brain, spleen, kidney, and lung.

BLASTOMYCOSIS

The yeast-like budding fungi, associated with some of the cases classed above under oïdiomycosis, are called by some writers *Blastomycetes*, and, therefore, such cases may be called blastomycosis.

In addition to these cases, however, a considerable number of observations of the occurrence of yeast-like fungi in a variety of pathological

[1] *Jour. Am. Med. Assoc.*, April 5, 1902, p. 867.
[2] Ibid., November 11, 1905, p. 1492

conditions both in man and animals are on record. Of these, there are only two isolated cases in man that seem worthy of mention. They are of a very different character from the cases grouped under oïdiomycosis and therefore, may be considered under blastomycosis. One of these cases[1] presented myxomatous tumors beneath the skin in several places. Histologically, the tumors resembled myxosarcoma and contained the fungi in large numbers. In the other case[2] sarcoma-like tumors involved the omentum and mesentery, and there was chylous ascites. In the ascitic fluid a yeast or blastomyces was found but in the tumors it was not satisfactorily demonstrated.

In animals several infectious processes are ascribed to blastomycetes. The most important of these is a suppurative disease in horses, resembling farcy, characterized by chronic inflammation of lymphatics and lymphatic glands in which there is proliferation and nodular thickening followed by purulent softening. The upper air passages are also involved.

SPOROTRICHOSIS

Definition.—An infectious and usually chronic disease chiefly affecting the skin and subcutaneous tissue, characterized by the formation of gumma-like nodes, abscesses, ulcers, and inflammatory infiltrations, cultures from which show a fungus or hyphomycete of the genus *Sporotrichium*. The lesions are usually multiple. It seems probable that some of the cases regarded as sporotrichosis were really cases of syphilis, or tuberculosis, or glanders, or other kinds of infection.

Schenck[3] reported the first case in 1898. De Beurmann[4] has done much to increase our knowledge concerning the disease and to facilitate its recognition. This account is drawn largely from his writings.

Etiology.—Sporotrichosis has a wide distribution throughout the civilized world. Hamburger[5] in a recent paper states that 28 cases proved by cultures from the lesions have been reported in the United States. The age of the patient and the season of the year do not seem to be of importance. More males than females have been affected. Wounds and abrasions, lowering of the resistance to infection by general debility or by wasting diseases, such as tuberculosis, may be regarded as predisposing causes, but in many cases the patients are otherwise healthy.

The fungus is thought to have a natural habitat in the outer world and to be widely distributed. Several species of the Sporotrichium have been described, but the differences among them do not seem to be important. The fungus occurs in cultures in the form of a branching septate mycelium with abundant formation of spores. The filaments of the mycelium are about 2 microns thick, have refringent walls and septa, and show refractive granules in their interior. The spores grow out along the sides and at the ends of the filaments, and are frequently

[1] Curtis, *Ann. d. l'Inst. Pasteur*, x, 449.
[2] Corselli and Frisco, *Centralbl. f. Bakteriol.*, 1895, xviii, 368.
[3] *Bulletin of the Johns Hopkins Hospital*, 1898, ix, 286.
[4] "*Les Nouvelles Mycoses*," etc., Paris, Masson et Cie., 1912.
[5] *Jour. Am. Med. Assoc.*, 1912, lix, 1590.

grouped in clusters. They are oval or oblong or pear-shaped bodies, frequently presenting a double contour, and have dimensions varying from 2 to 5 microns or more. They are attached to the filaments by delicate pedicles and are easily shaken off. With basic aniline dyes and with Gram's method of staining they stain generally evenly but sometimes show vacuole-like areas. The filaments do not stain as deeply as the spores and may show in their interior more deeply staining granules. The spores are not killed by a temperature of zero and 55° C.

The fungus grows on all the usual culture media, best on those containing sugar. It is aërobic and thrives as well at room temperature as in the incubator. The colonies on solid media are at first pale-gray or nearly white and have a delicate fringe of radiating filaments at their margins. Later they spread widely over the surface of the media and form a layer or a membrane one or more millimeters thick, with a wrinkled surface which may become brown or black in color. In stab cultures lateral outgrowths occur along the line of inoculation. Gelatin is slowly liquefied by the organism. In bouillon the organism grows as a downy sediment. The growth in the original cultures from the lesions may be slow, the colonies appearing only after a week or more. In succeeding generations the growth is more rapid.

The organism is pathogenic for experimental animals, especially for white rats. In the latter animals, septicemia and disseminated suppurative or granulomatous lesions may be produced by inoculation with cultures. The testicles are very frequently involved after intraperitoneal inoculation. In the experimental lesions the organism does not appear in the filamentous form, but only in modified forms, more or less resembling the spores and as oblong Gram-staining bodies 1 to 3μ wide and 10 to 12μ long. Sometimes small bud-like processes project from these forms.

It is claimed that spontaneous infection with *Sporotrichium* has been observed in the dog and rat, and that some of the cases of epizoötic or mycotic lymphangitis in horses are due to infection with this organism. In several instances sporotrichosis has occurred in individuals who had been in contact with horses affected with lymphangitis. In man, instances of apparent contagion are very rare and epidemics are not known.

Pathology.—The most characteristic anatomical feature of sporotrichosis is the formation of gumma-like nodules in the subcutaneous tissue which break down and become abscesses. Histologically the lesions show, besides suppuration, granulation-tissue formation with giant cells and masses of epithelioid cells. They have so much resemblance to those of tuberculosis, syphilis and other inflammatory processes that they cannot be distinguished from them. In human lesions, the recognition of the fungus elements in the pus or in the tissue is difficult or impossible because they appear to exist therein in modified forms which generally cannot with certainty be distinguished from fragments of cells, etc.

Clinical Forms.— *Disseminated Gummatous Sporotrichosis.*—A "gumma" appears at first as a small spherical, hard, elastic, movable, painless nodule not exceeding 5 or 6 mm. in diameter situated in the subcutaneous tissue. In the course of some weeks the nodule grows and may attain

a diameter of 20 to 30 mm., elevating the skin to which it becomes adherent. The skin over it then becomes pink to purplish in color. In the course of about two weeks more, the nodule softens and contains at first a transparent viscid fluid streaked with pus; later the fluid is opaque, thick, and purulent. It does not totally break down, the softening occurring only in the central portions, and the abscess thus resulting is usually cold and painless. Perforation of the skin and the formation of an ulcer may or may not take place later. An ulcer does not involve all of the nodule, but some of the tissue of the nodule persists. Inflammation of the lymph nodes is rare.

The number of gummata and ulcers varies, in general, between 4 and 35, but more than 100 have been observed. They may be widely disseminated, show no regularity of distribution, and may affect any part of the body. Their appearance may be more or less simultaneous, but usually they appear one by one, one to three weeks apart.

In certain cases extracutaneous lesions have been observed, among which may be mentioned the following: ulcerative and papillomatous inflammations of the throat; gumma-like lesions in the muscles; periostitis; osteitis; osteomyelitis; synovitis; inflammation of the ocular tissues; and abscess of the epididymis.

Localized Sporotrichosis—In this form the sporothrix is supposed to gain entrance through a wound in the skin where it causes an initial lesion or "chancre" from which the infection travels by the lymph channels centripetally and causes induration and the formation of gummata, abscesses and ulcers along their course for variable distances. There may or may not be inflammation of the lymph nodes. Generally the infection atrium is demonstrable, but it may escape observation. Rarely there is found only the initial lesion with or without swelling of the lymph nodes. The upper extremity is most frequently affected. The period of incubation is stated to be six days or longer.

Whatever be the form of sporotrichosis, its course is almost always chronic and the general conditions of the patient seems but slightly influenced by the infection in most cases. In rare cases anemia and emaciation seem to have been produced by it. In a very few instances the onset and course has been that of an acute septicemia, with fever, chills, nausea, epistaxis, and simultaneous development of the lesions.

Diagnosis.—As the lesions of sporotrichosis cannot be distinguished from those of syphilis, tuberculosis, oïdiomycosis, glanders, farcy, or other pyogenic infections, the only method of diagnosticating the disease is by the cultivation of the sporothrix from the pus or substance of a lesion. De Beurmann also recognizes as a means for diagnosis the agglutination test with the spores of the organism. Portions of a culture are ground up in a mortar and a suspension made in normal salt solution. This is filtered through filter paper previously wet. The filtrate contains only the spores, the mycelium being removed by the filtration, and to this filtered suspension the serum of the patient is added in proportions varying from 1 to 150 to 1 to 800. In cases of sporothrichosis the agglutination or aggregation of the spores into clumps usually occurs at dilutions of 1 to 300 or 400, in the course of fifteen to sixty minutes.

Prognosis.—This is usually good if proper treatment is given. Deaths have occurred usually only in cases affected with some other disease.

Treatment.—The basis of this is the internal administration of iodides and dressing the lesion with iodine and potassium iodide. Potassium iodide or similar compounds should be given in increasing doses up to 6 gms. (90 gr.) or more per day. If this cannot be borne by the stomach, rectal administration may be tried. The administration of the iodides ought to be continued for a month after apparent recovery to prevent possible recurrence and relapse. Abscesses should not be opened unless they show no tendency to resorption and then they should not be incised but evacuated by puncture and aspiration. Weak solutions of iodide may be injected thereafter. Ulcers should be cauterized with tincture of iodine and poulticed with a solution consisting of water 500 cc. (℥xv) potassium iodide 10 gm. (gr. cl); iodine 1 gm. (gr. xv).

PULMONARY ASPERGILLOSIS

Definition.—A destructive inflammatory process affecting the lungs due to infection with one or more species of fungus of the genus Aspergillus. The first observation of the occurrence of a fungus that was probably an aspergillus in a human lung was made by Bennett in 1842; but the first scientific description of cases with an exact determination of the identity of the fungus was by Virchow in 1856.

Etiology.—The disease is due to infection with the spores of the microörganism, and the species fumigatus is probably the only one concerned. The spores gain entrance to the lung through the respiratory tract. The *Aspergillus fumigatus* is a true fungus belonging to the family Perisporeacea. In cultures it grows in the form of a mould consisting of a thick felt-work of septate tubular hyphæ, a few microns in diameter, some of which grow upward into the air and produce masses of spores at their free extremities. The spores are spherical, 2.5 or 3.5μ in diameter and are easily transported through the air. The various species of aspergillus are common in the outer world and the spores are widely distributed on vegetable material of all kinds.

The *Aspergillus fumigatus* has been found as a harmless parasite in the auditory canal, tympanum, nose, mouth, maxillary sinuses, throat, respiratory passages, eyes, and genitalia. Sometimes it is found in an inflammatory condition of the external auditory canal, but the inflammatory process in these cases is probably due, in part at least, to the action of pyogenic bacteria. It is said to be capable of causing keratosis, dermatitis, a peculiar affection of the nails, rhinitis, and pharyngitis.

In various birds, and in cattle, horses, and dogs, it may be the cause of an inflammatory process more or less resembling tuberculosis in which the lesions are situated chiefly in the lungs. In birds, the liver, the kidneys, and the air sacs may also be infected and it may produce a pseudodiphtheritic condition of the mouth and air passages. The intravenous inoculation of birds and various animals with spores may produce death within a few days. The lesions produced resemble grossly

those of tuberculosis. Histologically, they consist of foci of necrosis, enclosing the microörganisms, together with more or less infiltration with inflammatory cells. Infection may be produced by way of the respiratory tract in birds, and rabbits may be infected by feeding.

Most of the cases of pulmonary aspergillosis in man may be regarded as instances of secondary infection in lungs already diseased by tuberculosis or other processes, and some have been mere terminal infections. But little clinical importance was attached to pulmonary aspergillosis until the observations of Dieulafoy, Chantemesse, and Widal,[1] published in 1890, and of Renon,[2] published in 1897, gave good grounds for believing that it could exist as a primary disease. These writers claimed that primary pulmonary aspergillosis was frequent among the so-called pigeon-feeders and hair-sorters of Paris. The pigeon-feeders are accustomed to feed the pigeons from their own mouths with a mixture of millet and vetch seeds in water. They are supposed to acquire the disease either from these seeds or from aspergillosis in the birds. The hair-sorters work in an atmosphere charged with the dust of rye flour, which they use in considerable quantities to free the hair from grease. Birds kept in this atmosphere died in two or three days from aspergillosis. The spores of the aspergillus are in the rye flour used and they gain entrance to the lungs directly from the air.

Special Pathology.—The essential lesions in the lung tissue are necrosis and exudation of leukocytes. The typical appearances are areas of pneumonic consolidation, or necrosis with a colony of the fungus in the centre. When the colony is in close relation with a bronchus and has had a good supply of oxygen, spores are produced which may be disseminated through the lung by way of the bronchi and give rise to further extension of the process. Eventually the necrotic tissue may be sequestrated and expectorated, thus giving rise to cavities with gangrenous walls. Usually bacteria do not take part in the necrotic process, and purulent liquefaction of the necrotic tissue does not occur. In typical cases there is little fetor associated with the process. It would seem that the fungus inhibits the invasion of the putrefactive bacteria into the lesions.

The microörganism may exist in the lesions in colonies, with a form suggestive of actinomyces; or the hyphæ may penetrate the diseased tissue more or less diffusely. The process in the lungs may become arrested and the fungus may disappear. In this case extensive fibroid changes may result, or the lungs may become the seat of tuberculosis. Metastatic lesions are not known to occur in aspergillosis.

Symptoms.—The clinical course in the primary cases is either that of chronic pulmonary tuberculosis or of chronic bronchiolitis, emphysema, and chronic interstitial pneumonitis. In secondary cases symptoms referable to the infection with aspergillus may be absent or slight.

Diagnosis.—This can only be made by finding fragments of the aspergillus or its spores in the sputum. Cultures may be necessary to establish the identity of the microörganism. The fragments of the

[1] *Tenth International Medical Congress*, Berlin, 1890.
[2] *Étude sur l'Aspergillose chez les Animaux et chez l'Homme*, Paris, 1897.

microörganism may be found imbedded in blood clots or in masses of necrotic tissue. The sputum may resemble that of pulmonary gangrene, but the characteristic fetor is absent. Tubercle bacilli may be found coincidently in the sputum. It is important that the sputum be fresh, for it may be secondarily invaded by spores of the aspergillus from the air. Microscopic examination of the sputum for the fungus is facilitated by mixing a small amount of it with a 20 per cent. solution of sodium hydrate in order to dissolve the cells and tissue fragments and render the fungus elements more clearly visible.

Prognosis.—When aspergillosis is engrafted upon a chronic disease of the lungs, it usually does not seem to contribute much to the death of the individual. In primary cases the prognosis is not so bad as in pulmonary tuberculosis, but even if the aspergillosis is arrested and disappears, the permanent injury to the lungs may lead to eventual death or may be followed by pulmonary tuberculosis. Cases resembling emphysema and chronic bronchiolitis seem to have a worse prognosis than those resembling pulmonary tuberculosis.

Treatment.—In the primary cases it is of the utmost importance that the patient avoid breathing in a dust-laden atmosphere or contact with dry grains and vegetable material. The main reliance should be placed upon fresh air, good food, and tonics. The internal administration of iodide of potassium or of arsenic has been advised. In the secondary form the treatment should be that of the underlying disease.

MYCOSIS MUCORINA

There is only one case on record of general infection with fungi of the genus *Mucor*. This was the case reported by Paltauf in which there was found at autopsy ulcerative enteritis, pneumonia, phlegmon of the pharynx, and multiple abscesses in the brain. In the lesions a mucor was found.

The mucors are moulds, a typical example of which is the common bread mould. Their spores, when injected into the circulation of certain animals, produce effects similar to those produced by the spores of *Aspergillus*.

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